Thirty new loci for age at menarche identified by a meta-analysis of genome-wide association studies

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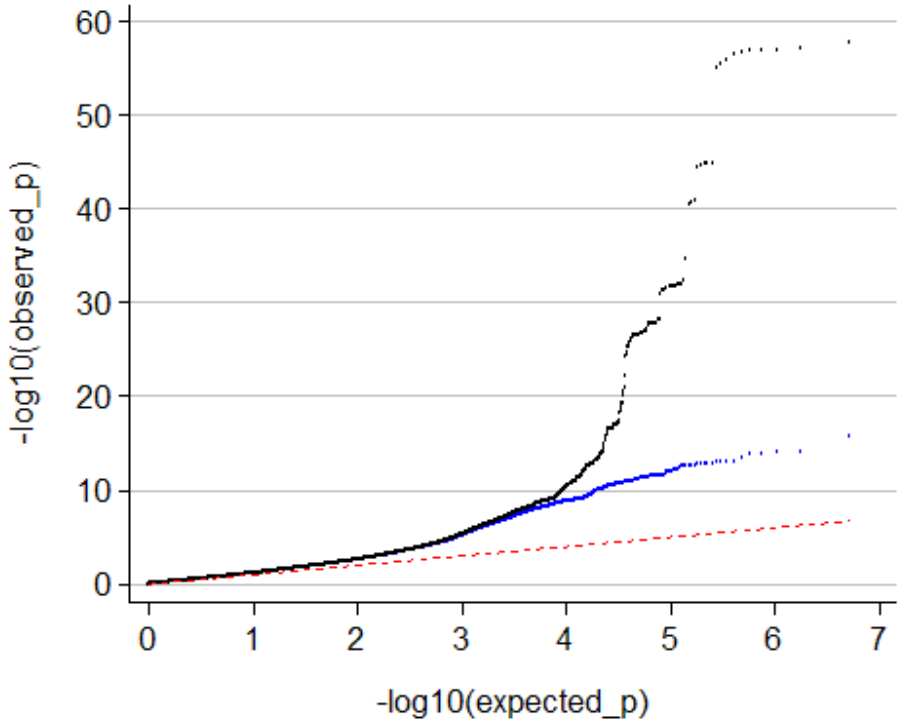
SUPPLEMENTARY INFORMATION

SUPPLEMENTARY FIGURE LEGENDS

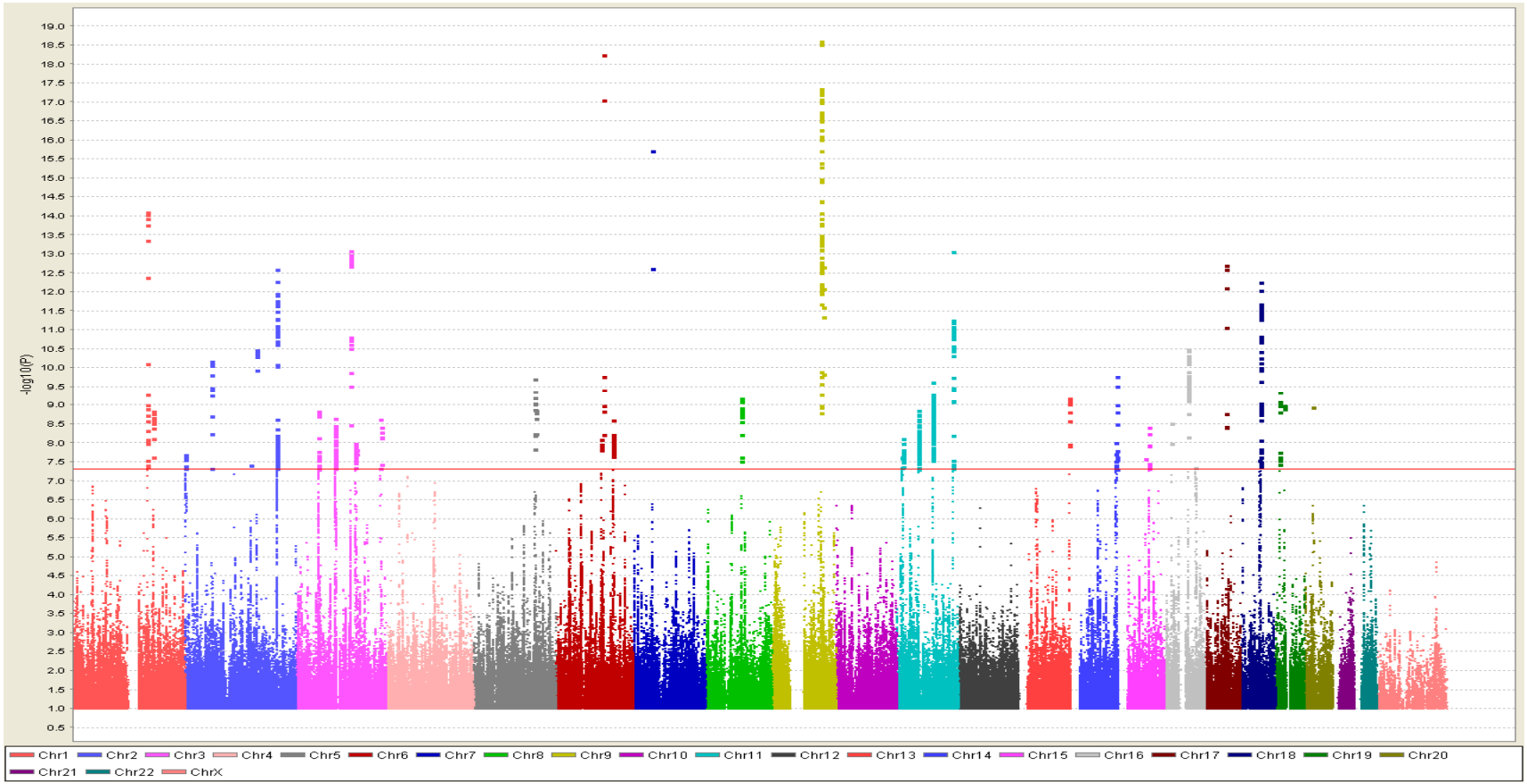
Supplementary Fig. 1: Quantile-quantile plots of the genome-wide scan for age at menarche.

The dots represent the observed –log10 *P*-values before (black dots) and after (blue dots) removal of signals associated with the two previously identified menarche loci at *LIN28B* and 9q31.2. The expected distribution of –log10 *P* -values under the null hypothesis is shown by the dashed red line.



Supplementary Fig. 2: Manhattan plot of GWAS for age at menarche from the Phase 1 meta-analysis of 32 studies.

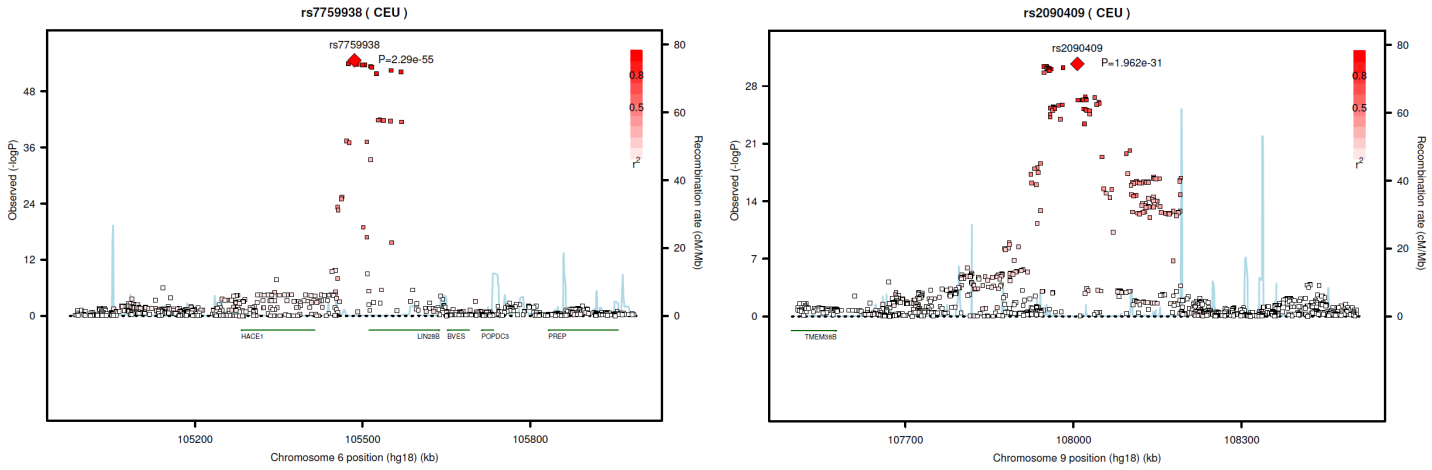
X-axis represents the chromosomal position for each SNP, and y-axis the –log10 P-value for association with age at menarche. Note: To highlight the novel menarche loci the y-axis is curtailed at –log10 P-value = 20, and therefore the strongest signals at the two previously identified loci on Chromosomes 6 and 9 are not displayed.



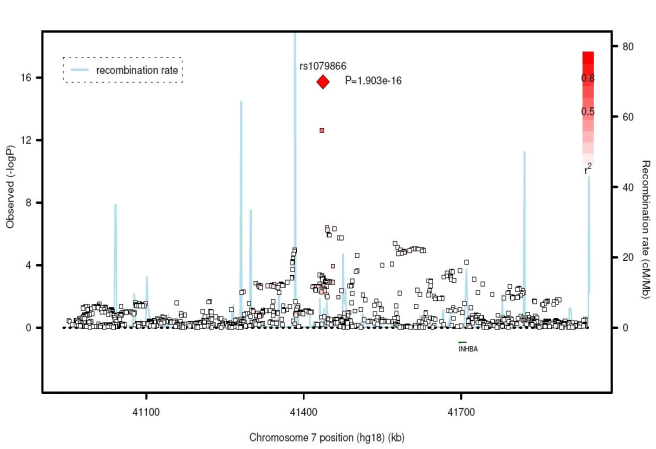
Supplementary Fig 3: Regional association plots for each of the 42 known, confirmed or possible novel menarche loci.

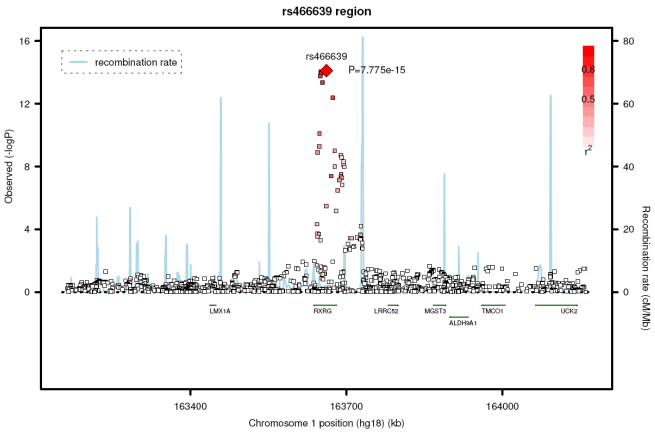
SNPs are plotted by chromosomal position (x-axis) against GWAS association with age at menarche (–log10 P value). The strongest signal is denoted by the figure sub-title and red diamond. Other SNPs are colour coded to reflect their LD with the top SNP (taken from pairwise r2 values from the HapMap CEU database). Estimated recombination rates (from HapMap) are plotted in cyan to reflect the local LD structure. Genes are denoted by green lines. Figures were drawn using SNAP LD (http://www.broadinstitute.org/mpg/snap/index.php#citation) except where indicated.

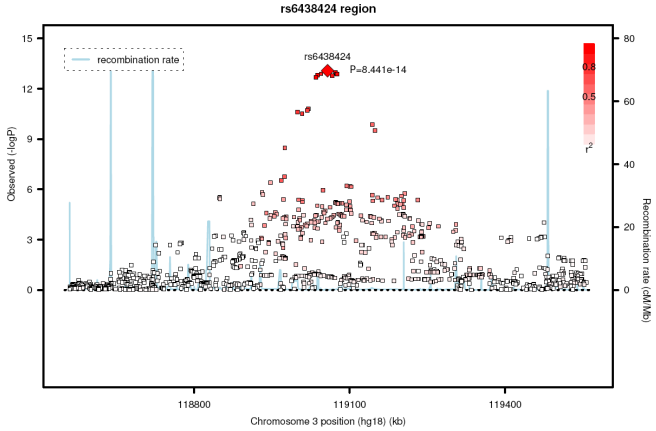
Two known menarche loci:

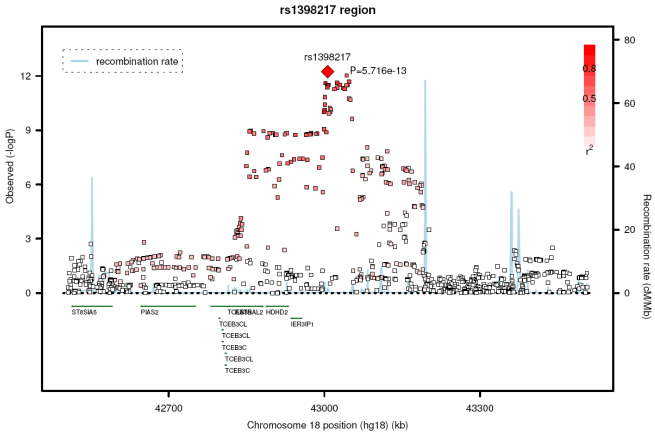


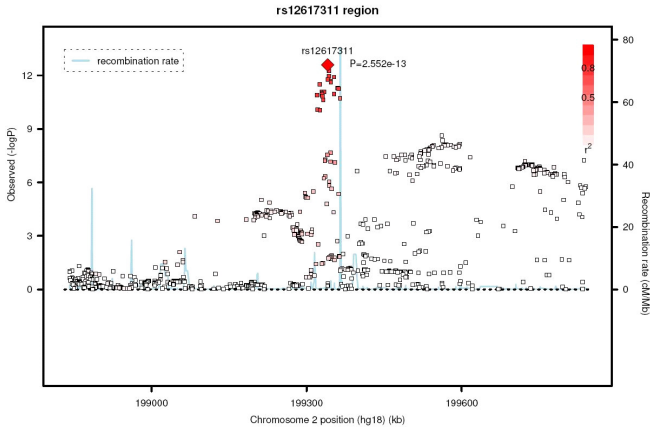
Thirty confirmed novel menarche loci:

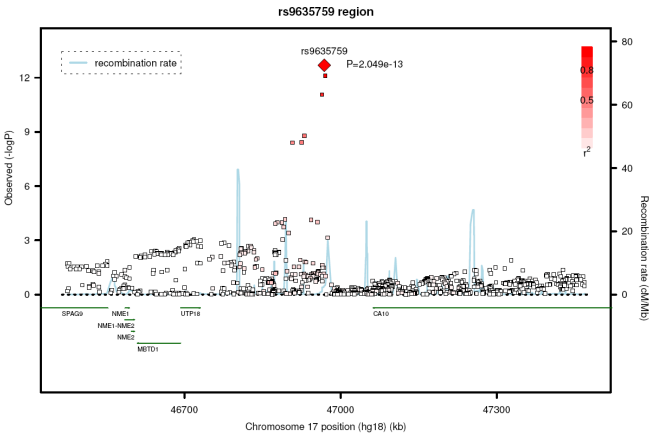


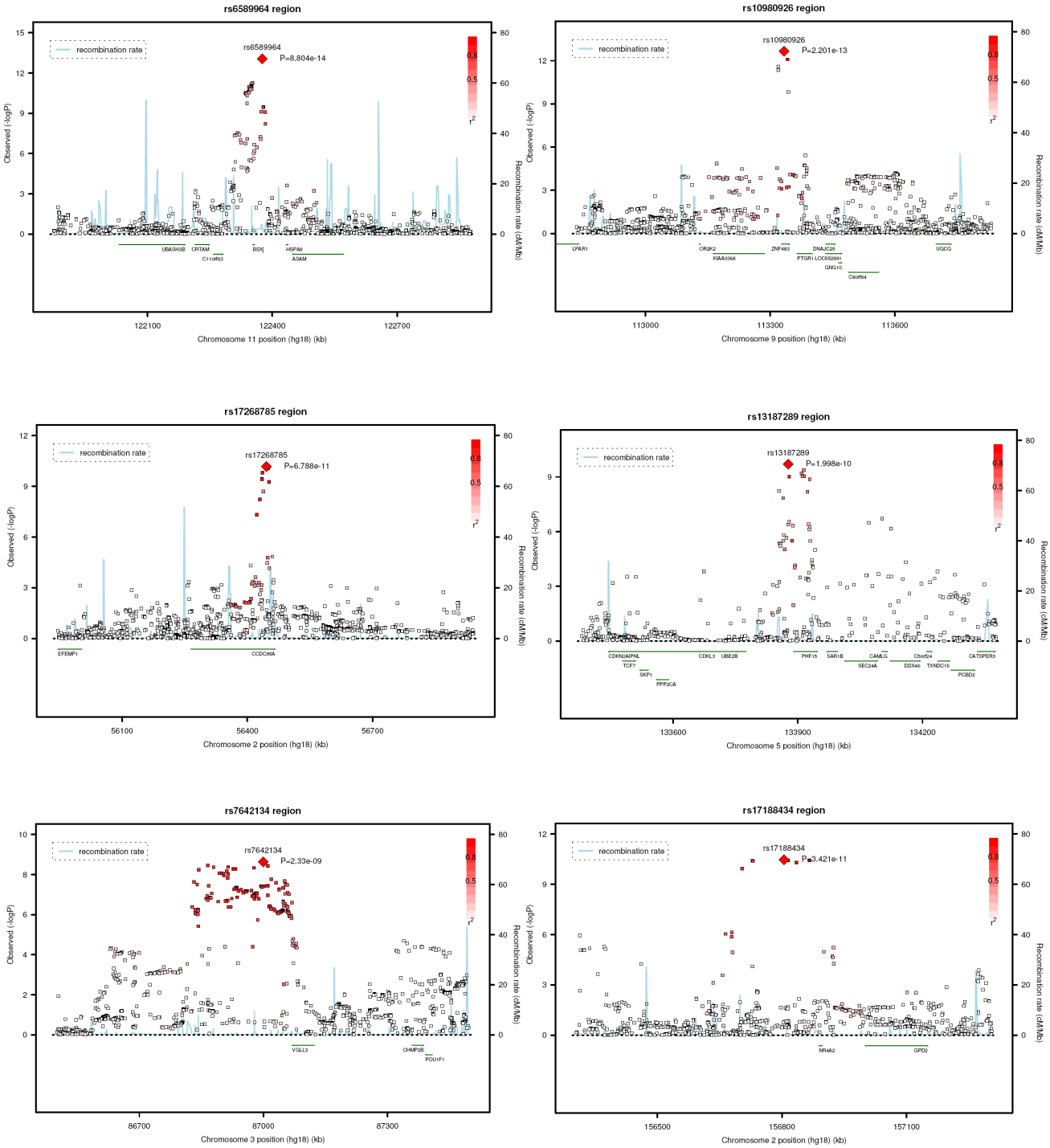


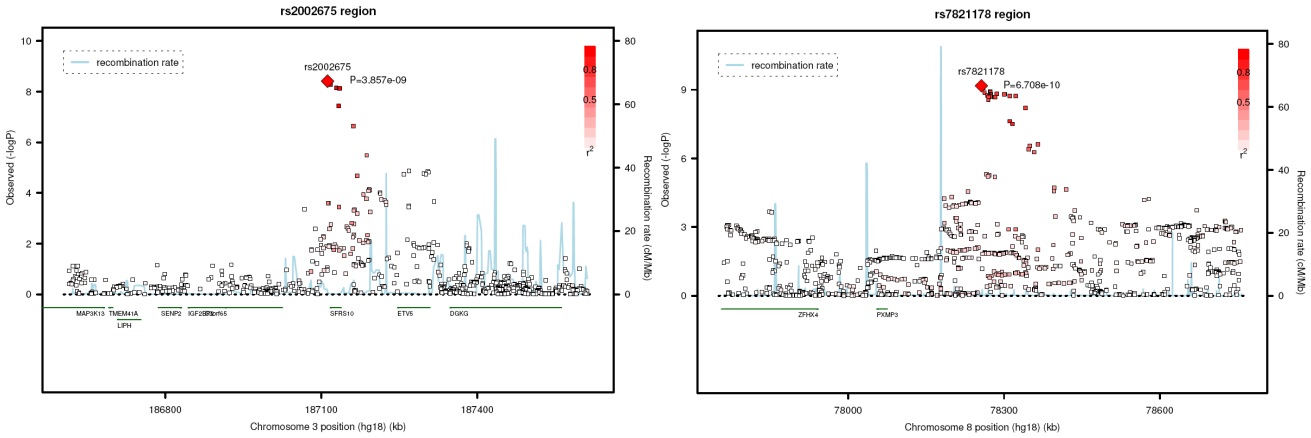


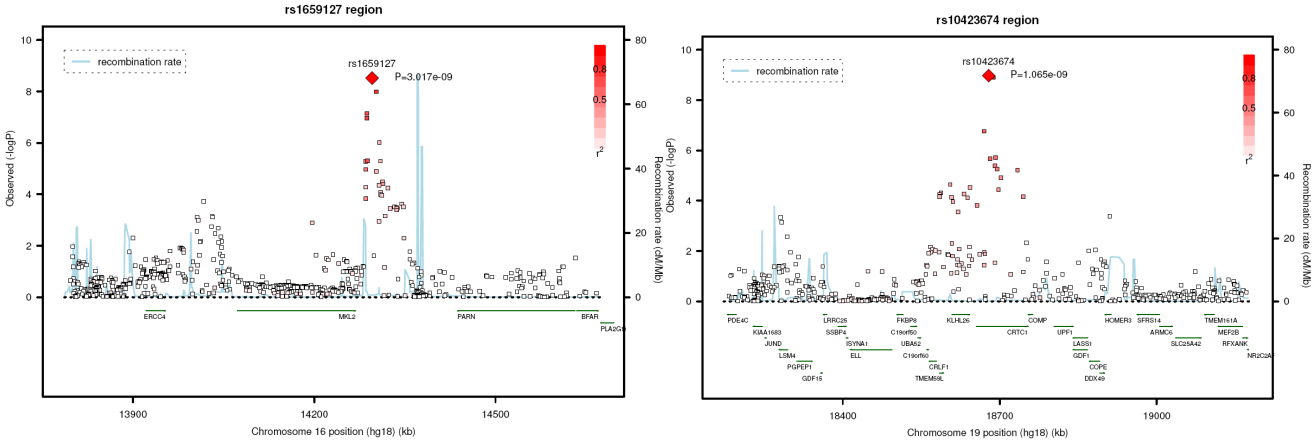


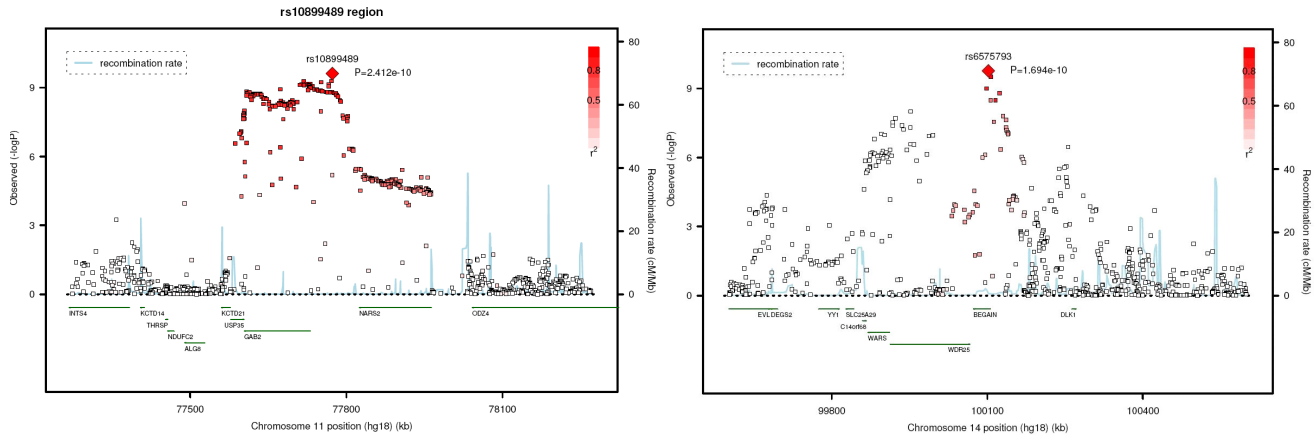




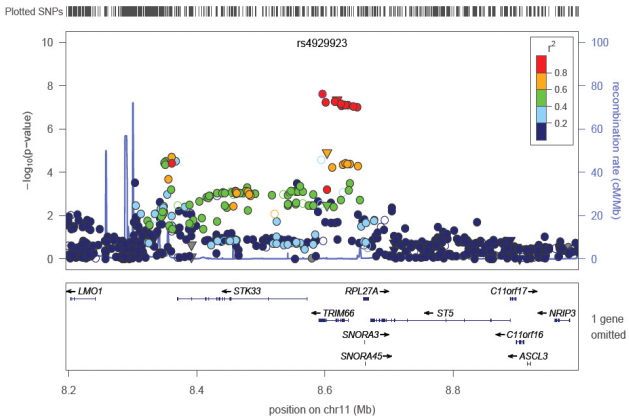

rs6589964 region
recombination rate
rs6589964
P=8.804e-14
Observed (-logP)
Recombination rate (cM/Mb)
Chromosome 11 position (hg18) (kb)
rs10980926 region
rs10980926
P=2.201e-13
Chromosome 9 position (hg18) (kb)
rs17268785 region
rs17268785
P=6.788e-11
Chromosome 2 position (hg18) (kb)
rs13187289 region
rs13187289
P=1.998e-10
Chromosome 5 position (hg18) (kb)
rs7642134 region
rs7642134
P=2.33e-09
Chromosome 3 position (hg18) (kb)
rs17188434 region
rs17188434
P=3.421e-11
Chromosome 2 position (hg18) (kb)

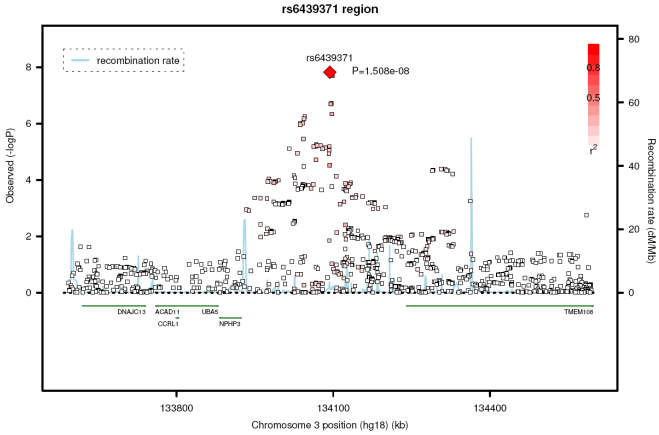

rs2002675 region
recombination rate
rs2002675
P=3.857e-09
Observed (-logP)
Recombination rate (cM/Mb)
Chromosome 3 position (hg18) (kb)
rs7821178 region
rs7821178
P=6.708e-10
Chromosome 8 position (hg18) (kb)

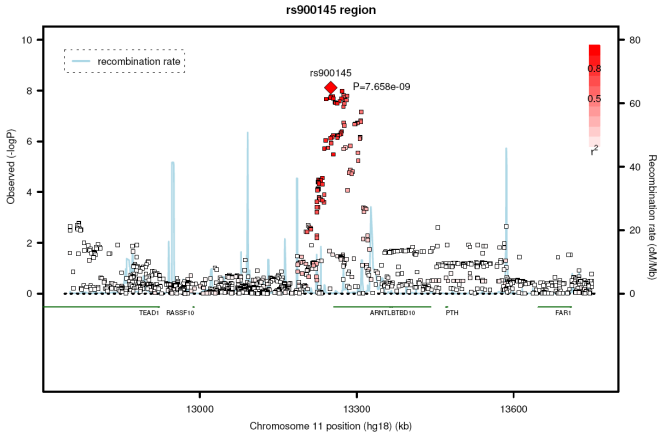

rs1659127 region
rs1659127
P=3.017e-09
Chromosome 16 position (hg18) (kb)
rs10423674 region
rs10423674
P=1.065e-09
Chromosome 19 position (hg18) (kb)

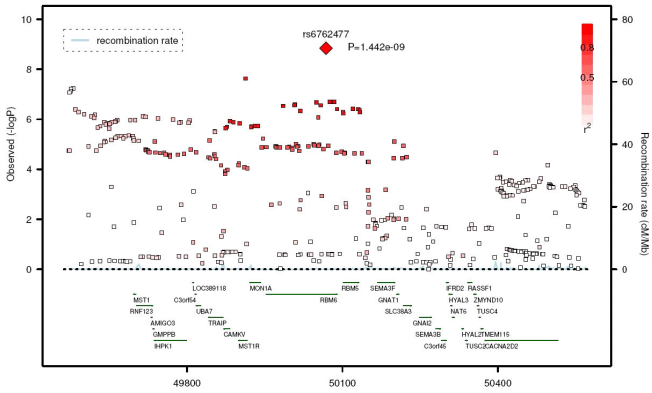

rs10899489 region
rs10899489
P=2.412e-10
Chromosome 11 position (hg18) (kb)
rs6575793
P=1.694e-10
Chromosome 14 position (hg18) (kb)

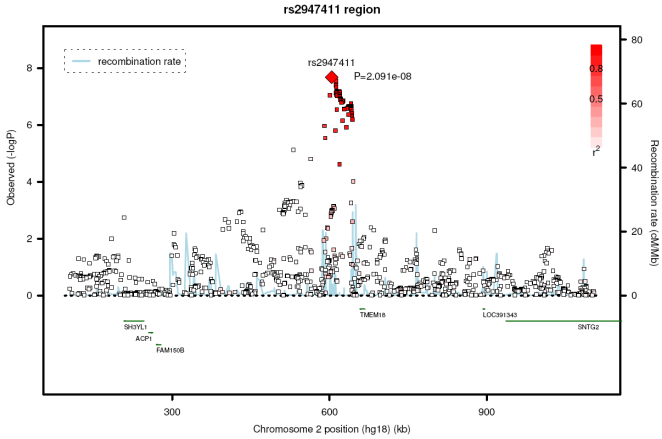
The rs4929923 region would not upload to SNAP and was drawn using LocusZoom (http://csg.sph.umich.edu/locuszoom/)

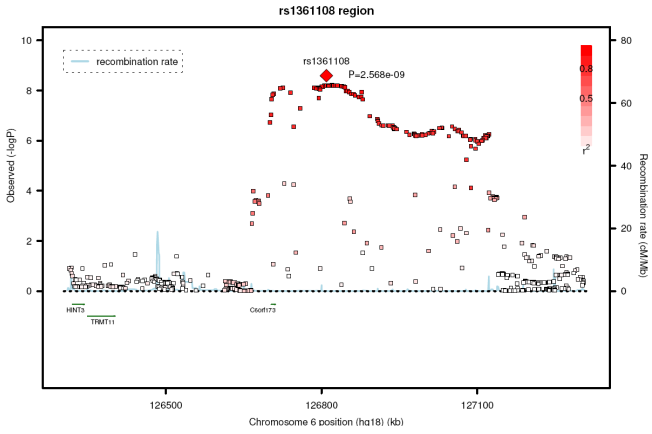


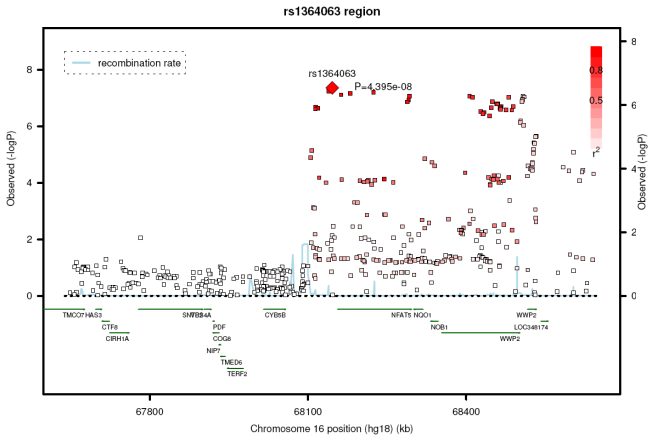








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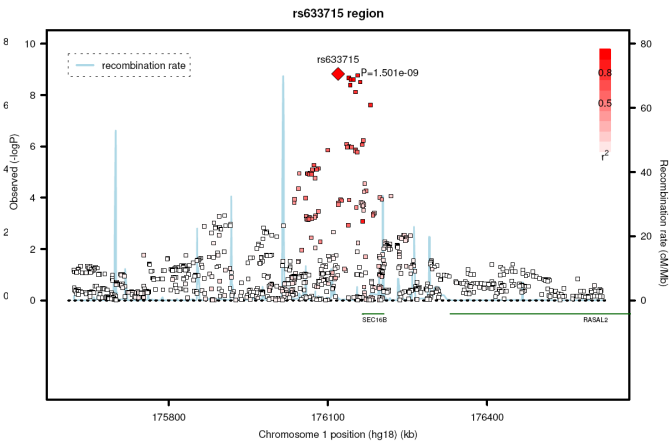
recombination rate
rs1364063
P=4.395e-08
Observed (-logP)
Recombination rate (cM/Mb)
Chromosome 16 position (hg18) (kb)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recombination rate
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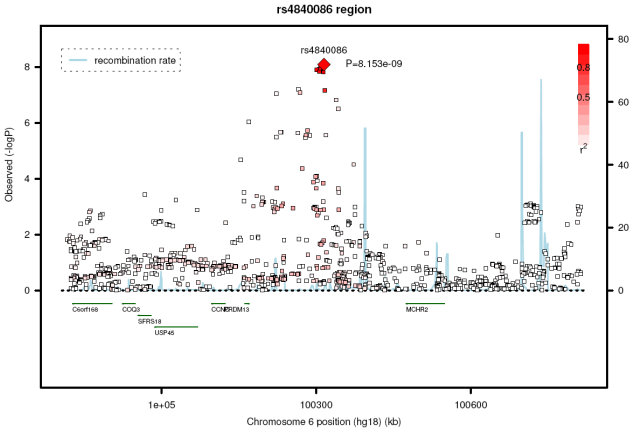
Observed (-logP)
Recombination rate (cM/Mb)
Chromosome 1 position (hg18) (kb)


rs4840086 region
recombination rate
rs4840086
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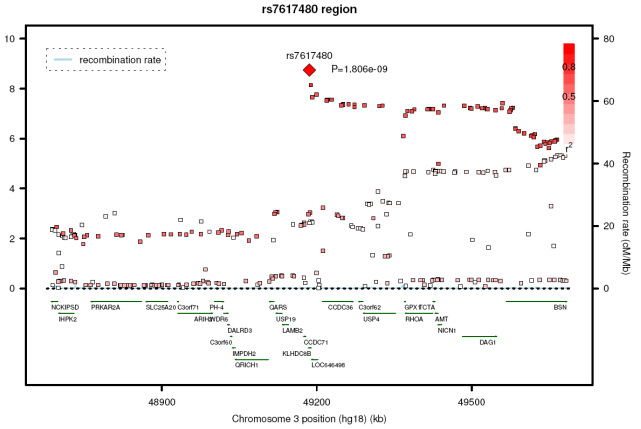
Observed (-logP)
Recombination rate (cM/Mb)
Chromosome 6 position (hg18) (kb)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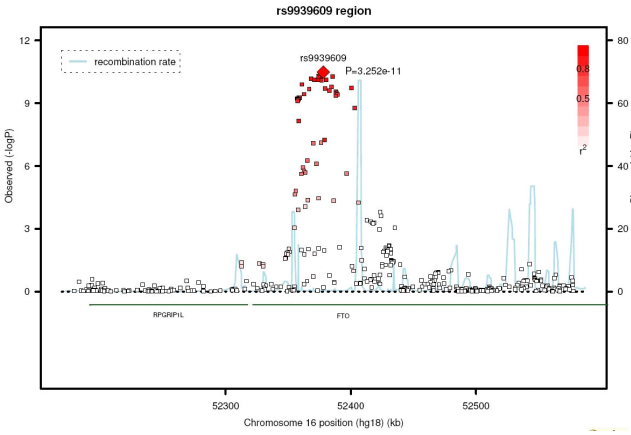
Observed (-logP)
Recombination rate (cM/Mb)
Chromosome 3 position (hg18) (kb)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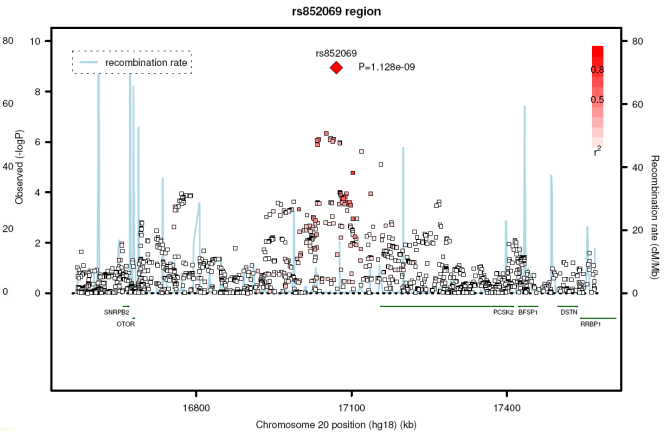
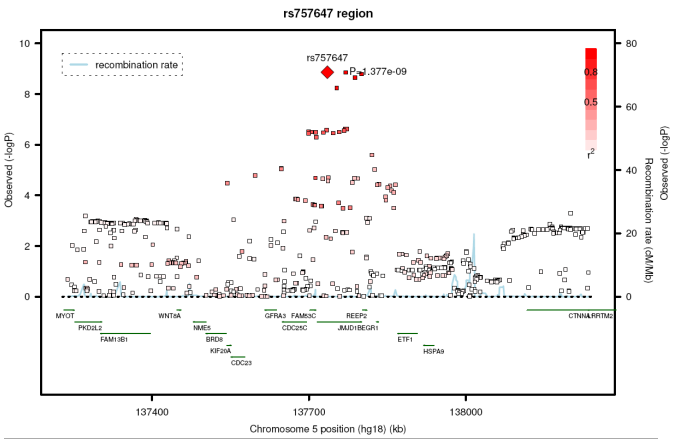
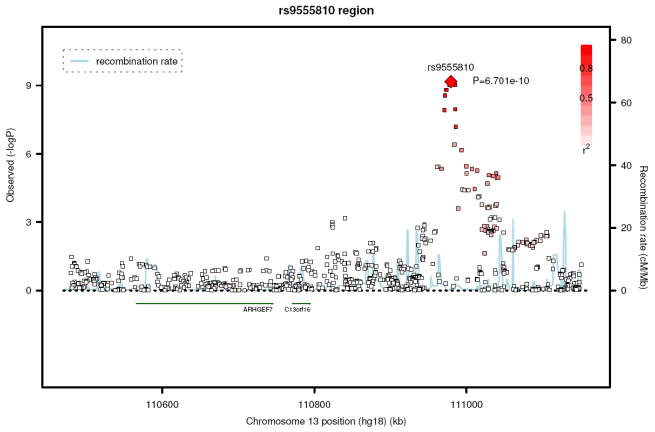
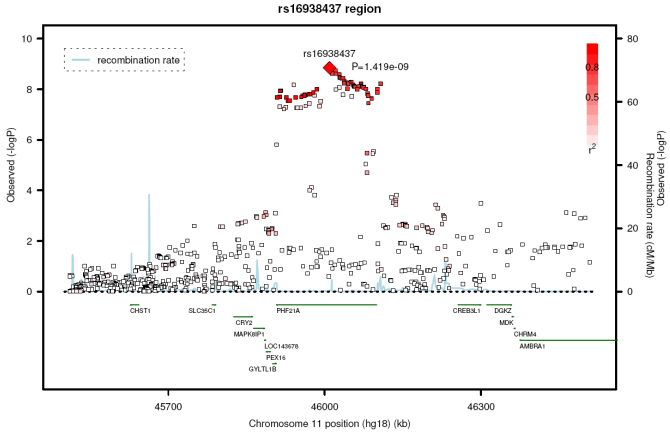
recombination rate
rs9939609
P=3.252e-11
Observed (-logP)
Recombination rate (cM/Mb)
Chromosome 16 position (hg18) (kb)

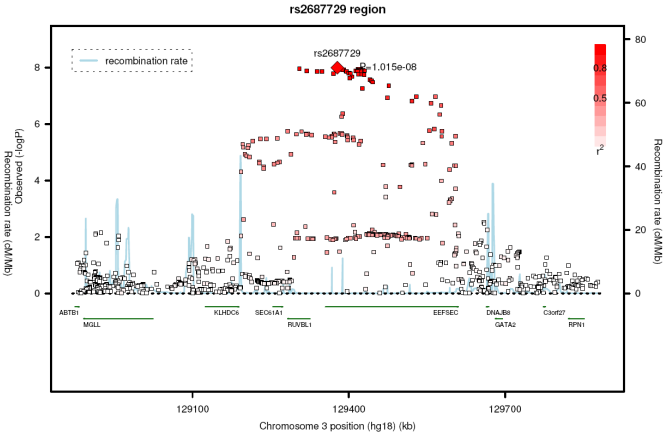

rs852069 region
recombination rate
rs852069
P=1.128e-09
Observed (-logP)
Recombination rate (cM/Mb)
Chromosome 20 position (hg18) (kb)

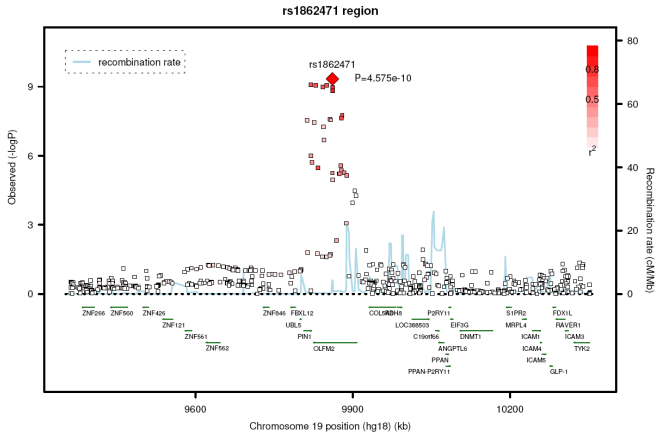
Ten possible novel menarche loci:

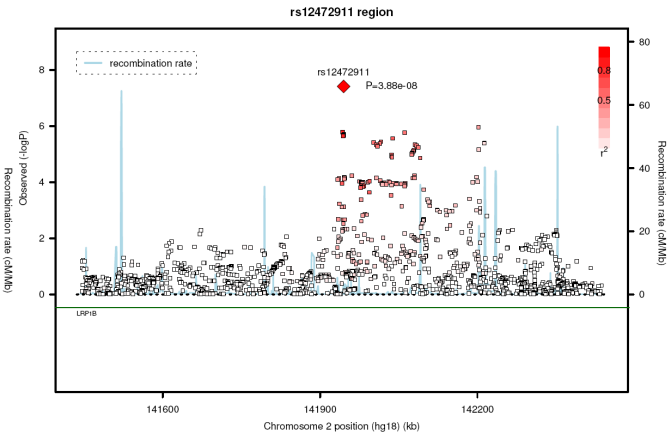


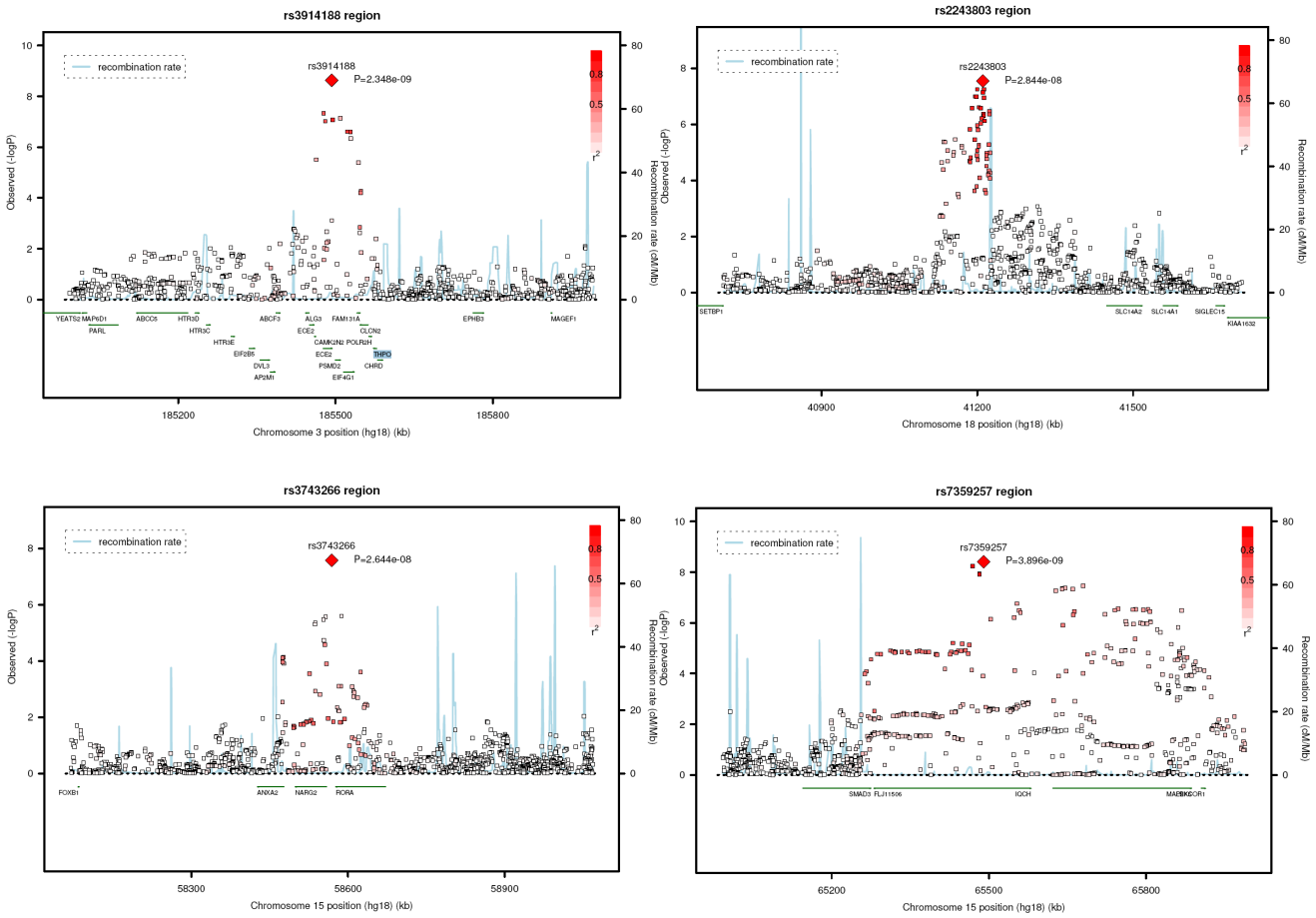






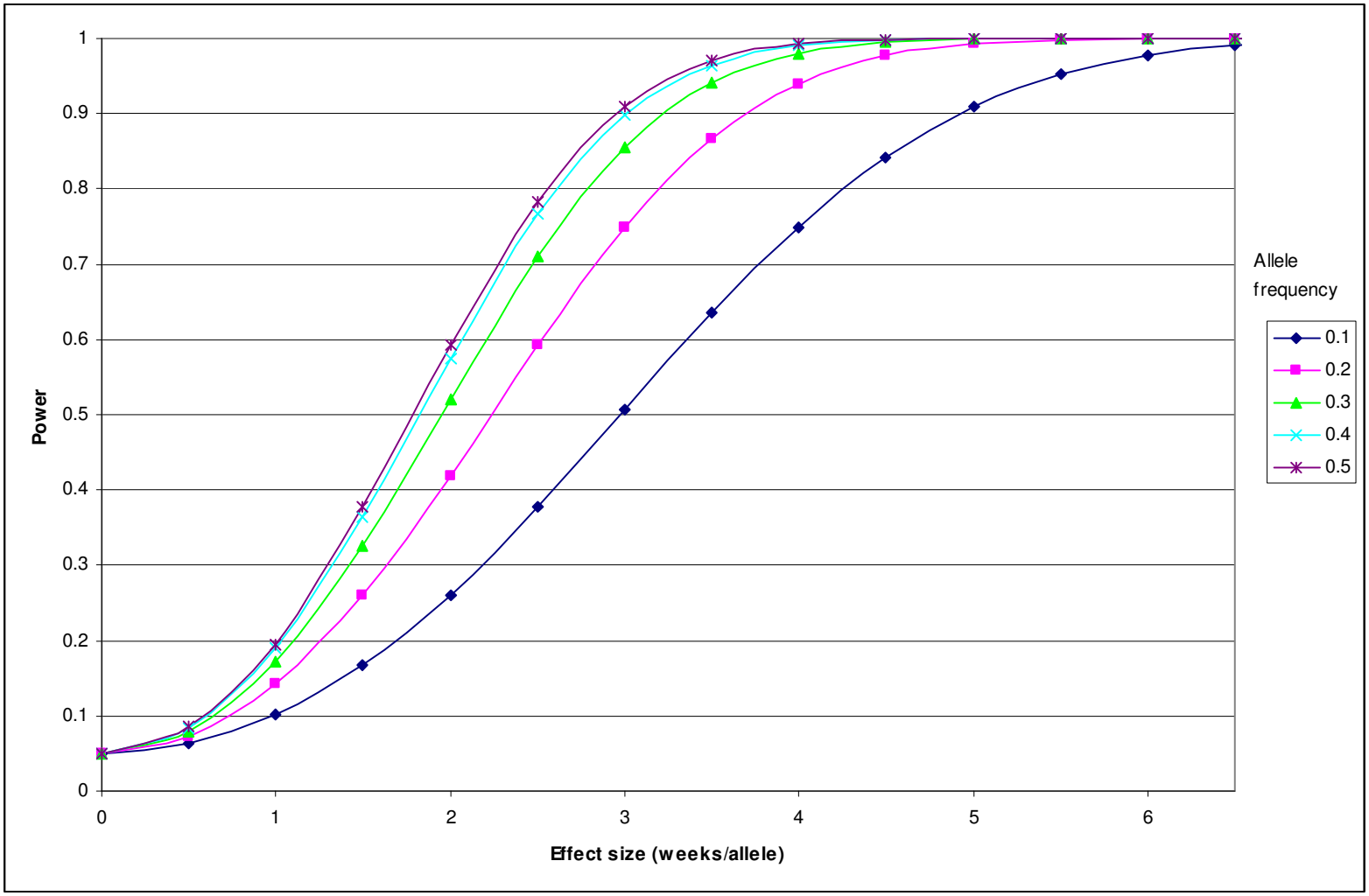





rs3914188 region
recombination rate
rs3914188
P=2.348e-09
Observed (-logP)
Recombination rate (cM/Mb)
Chromosome 3 position (hg18) (kb)
rs2243803 region
rs2243803
P=2.844e-08
Chromosome 18 position (hg18) (kb)
rs3743266 region
rs3743266
P=2.644e-08
Chromosome 15 position (hg18) (kb)
rs7359257 region
rs7359257
P=3.896e-09
Chromosome 15 position (hg18) (kb)

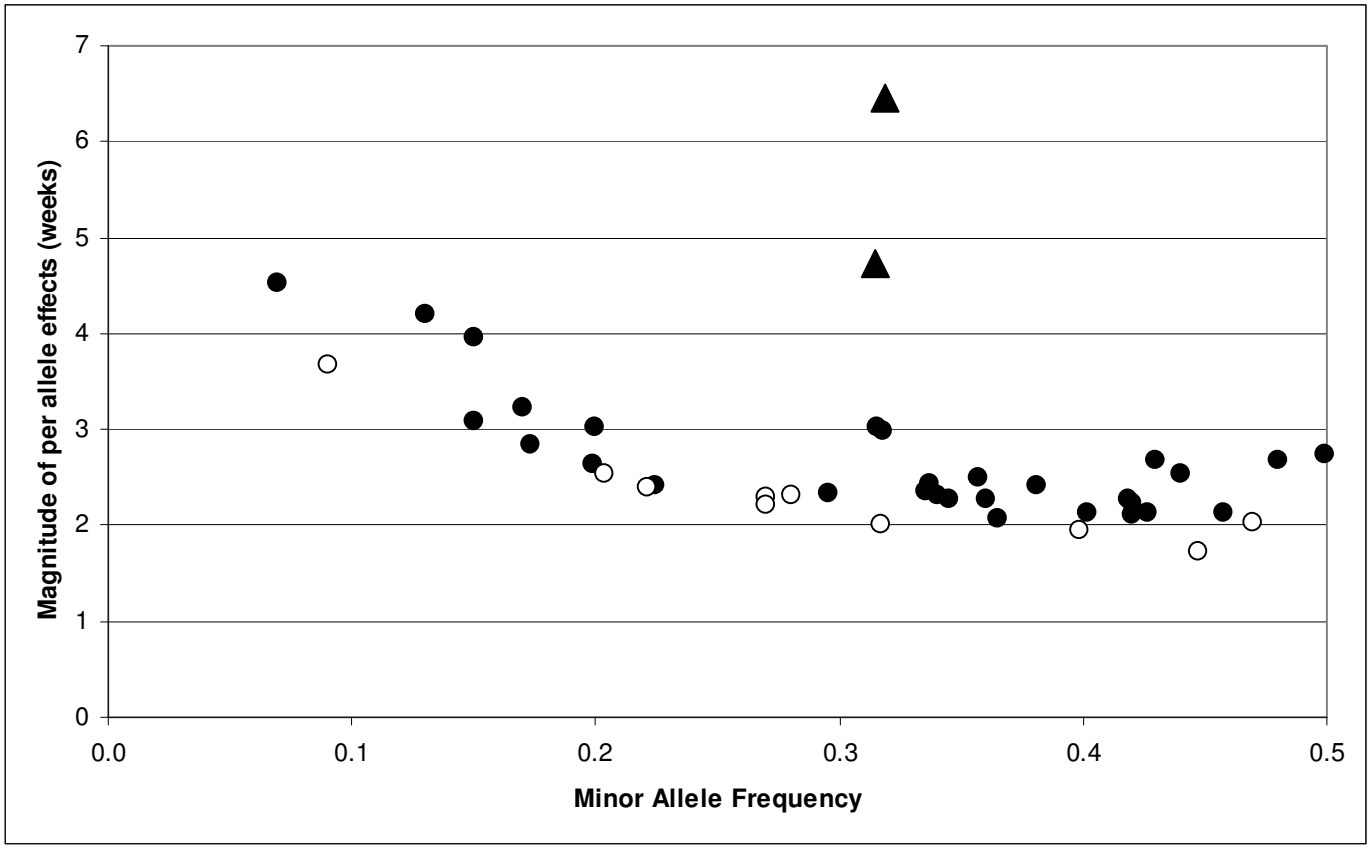
Supplementary Fig. 4: Statistical power of the age at menarche replication studies (n=14,731 women).

Based on age at menarche as a continuous outcome with mean ± SD 13 ± 1.5 years, additive models and 2-sided P<0.05.



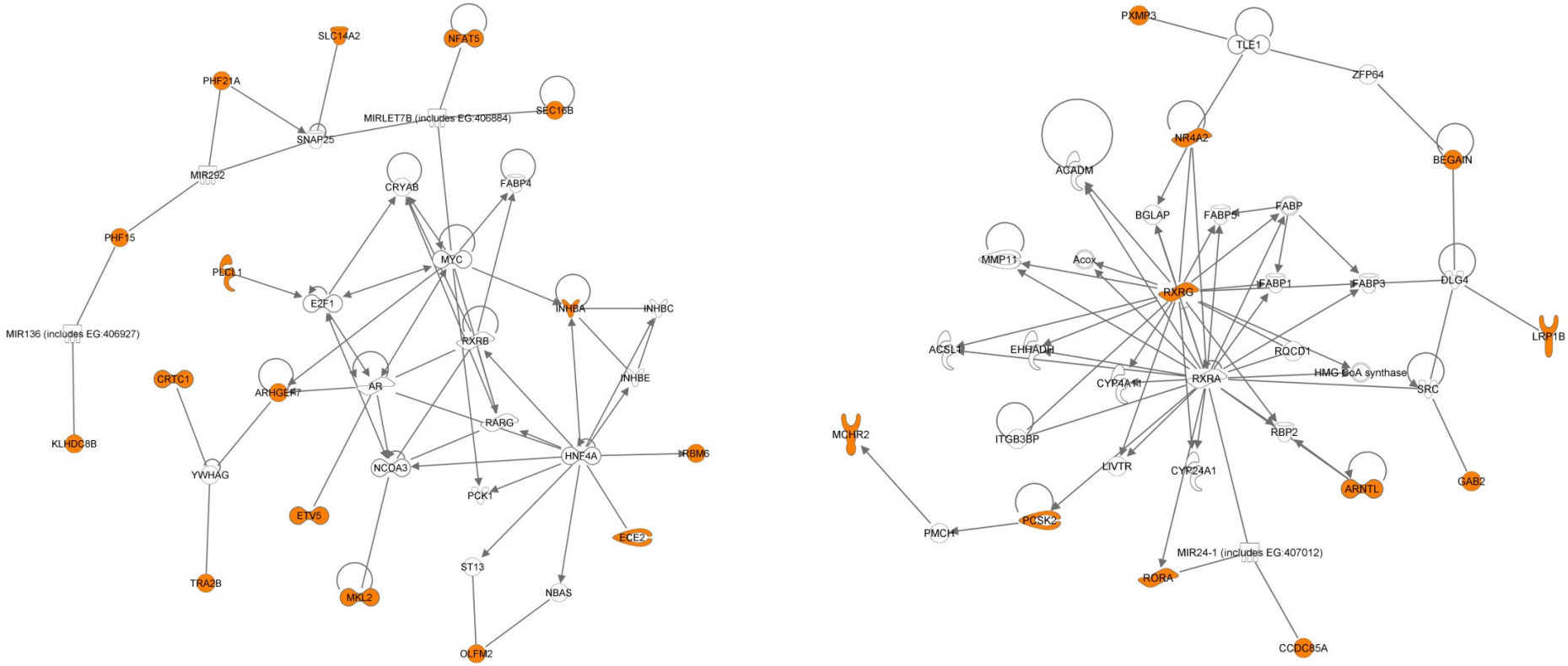
Supplementary Fig. 5: Estimated magnitude of per allele effects of the 42 known, confirmed or possible novel menarche loci plotted by minor allele frequencies.

The two known loci are indicated by triangles, the 30 confirmed novel loci by filled circles and the 10 possible novel loci by open circles.



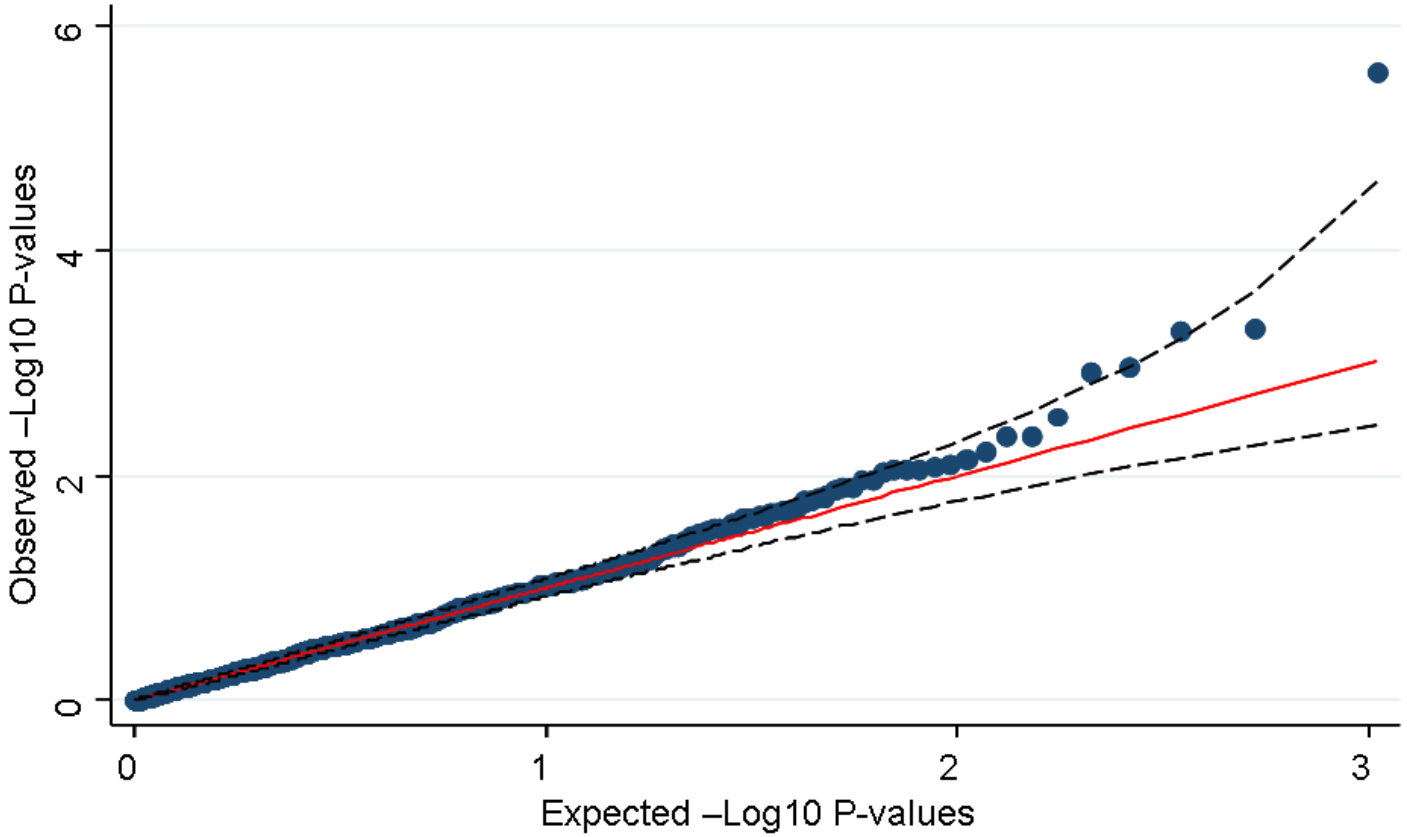
Supplementary Fig. 6A and 6B: Networks revealed through the Ingenuity Pathway Analysis.

Based on genes nearest to the 42 known, confirmed or possible novel menarche loci. A) Network 1, $p=1x10^{-37}$; B) Network 2, $p=1x10^{23}$. Molecules highlighted in orange represent the genes nearest to the menarche loci. Grey lines indicate the direct relationship between genes and molecules.



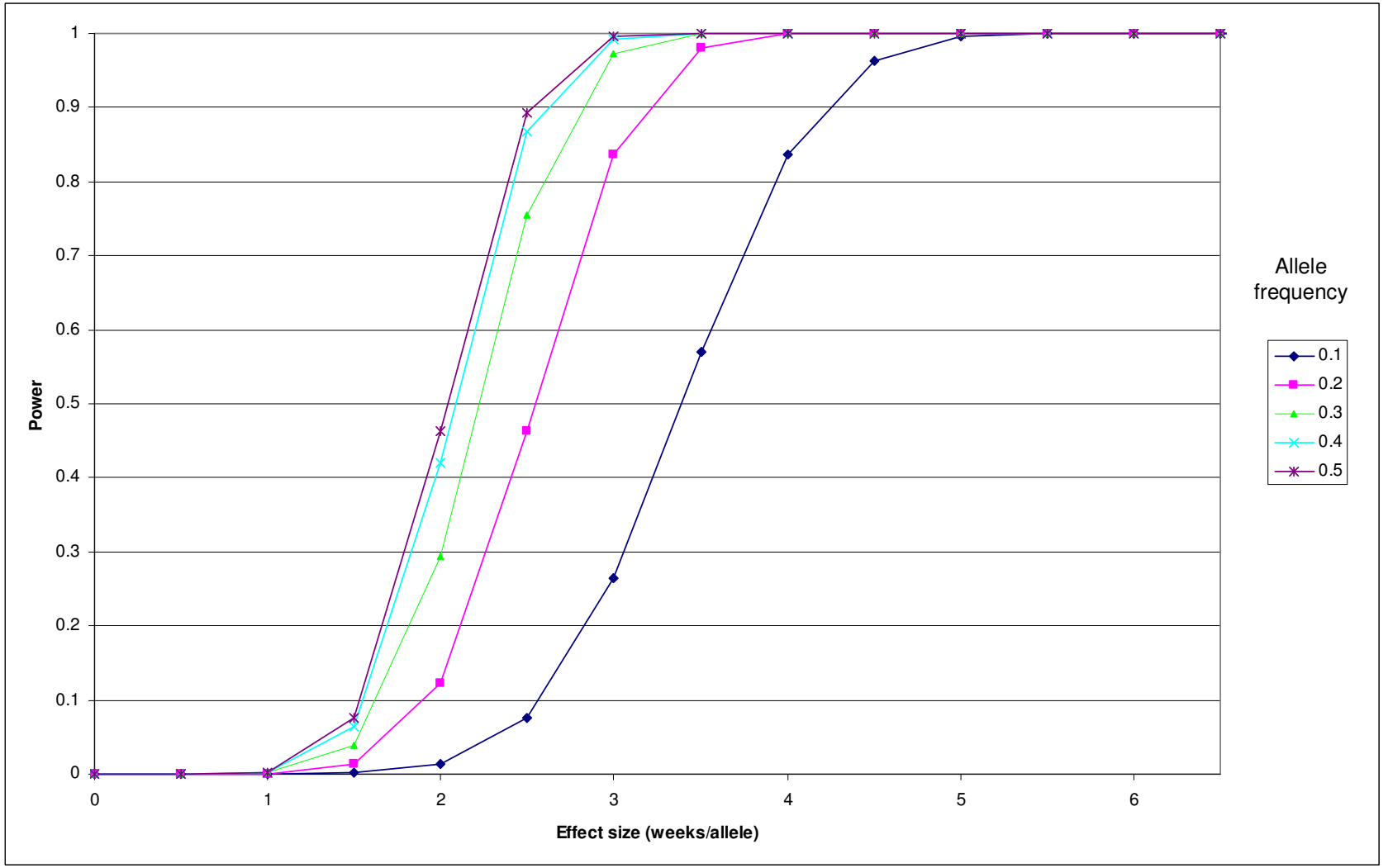
Supplementary Fig. 7: Quantile-quantile plot from the CNV tagging SNP scan.

Based on the list of CNV tagging SNPs (N=1052) from Conrad et al. Nature 2009 (Ref 25)
The only hit which survived multiple testing is at *NEGR1*, the known CNV locus for BMI (rs3101336, MAF 0.39).



Supplementary Fig. 8: Statistical power of the phase 1 meta analysis for age at menarche (n=87,802 women).

Based on age at menarche as a continuous outcome with mean ± SD 13 ± 1.5 years, additive models and 2-sided $P<5x10^{-8}$.



Supplementary Table 1: Details of the 32 studies that contributed to the Stage 1 GWAS meta-analysis with age at menarche.

Study name/acronym	*Full study name*	*N*	GC Factor	*Mean age (SD)*	***Mean AAM (SD)***	*Specific menarche questions*
AGES-Reykjavik	Age, Gene/Environment Susceptibility Study	1849	1.03	76.3 (5.5)	13.6 (1.3)	*"At what age did your menstrual periods begin?"*
Amish	The older order Amish population studies	557	1.046	49.1 (3.7)	13.1 (1.3)	*"How old were you when you had your first menstrual period?"*
ARIC	Atherosclerosis Risk in Communities Study	4247	1.028	53.9 (5.7)	12.9 (1.5)	*"At approximately what age were you when your menstrual periods started?"*
B58C-T1DGC	British 1958 birth cohort (Type 1 Diabetes Genetic Consortium controls)	1021	1.018	16.1 (0.2)	12.7 (1.4)	*Question asked to parents (usually mother): "At what age did she have her first menstrual period?" Answers were coded as "before 11th birthday" (we coded as 10), "when aged 11", "aged 12", "aged 13", "aged 14", "aged 15 or more", "not yet commenced" (which we coded as 16), "commenced but don't know when" (excluded), "don't know if commenced" (excluded).*
B58C-WTCCC	British 1958 birth cohort (Wellcome Trust Case Control Consortium controls)	563	0.998	16.1 (0.2)	12.8 (1.3)	*Question asked to parents (usually mother): "At what age did she have her first menstrual period?" Answers were coded as "before 11th birthday" (we coded as 10), "when aged 11", "aged 12", "aged 13", "aged 14", "aged 15 or more", "not yet commenced" (which we coded as 16), "commenced but don't know when" (excluded), "don't know if commenced" (excluded).*
CoLaus	Cohort Lausannoise	2797	1.03	53.4 (10.8)	13.2 (1.6)	*At what age did you have your first period?*
deCODE	deCODE Genetics, Iceland	15,864	1.284	birth year 1948.1 (17.0)	13.2 (1.3)	*How old were you when your menstruation started?*
DNBC	Danish National Birth Cohort, Preterm delivery study	1748	1.023	30.0 (4.3)	13.3 (1.3)	*"How old were you when you had your first menstrual period?"*
EGCUT	Estonian Genome Center, University of Tartu	987	1.02	41.2 (16.5)	13.4 (1.5)	*"How old you where when you had your first menstruation event?"*
EPIC-obesity cohort	European Prospective Investigation into Cancer and Nutrition - Obesity study cohort	1215	0.97	58.7 (9.0)	12.9 (1.8)	*"How old were you when you had your first menstrual period?"*
EPIC-obesity cases	European Prospective Investigation into Cancer and Nutrition - Obesity study cases	625	0.961	58.8 (8.8)	12.7 (2.0)	*"How old were you when you had your first menstrual period?"*
ERF	Erasmus Rucphen Family study	1103	1.032	47.5 (14.3)	13.1 (1.7)	*"At what age did your menstrual periods begin?"*
FHS	Framingham Heart Study	3801	1.013	42.5 (10.1)	12.8 (1.5)	*"Age at start of menses" and "How old were you when you had your first menstrual period (menses)?" "About how old were you when you had your first menstrual period?"*
HBCS	Helsinki Birth Cohort Study	976	1.006	61.5 (3.0)	12.8 (1.5)	*"At what age did your menstrual periods start?"*
Health 2000 (Genmets) cases	Health2000 cohort - case subsample	457	0.999	51.8 (11.5)	13.4 (1.5)	*"How old were you when your periods started?"*
Health 2000 (Genmets) controls	Health2000 cohort - control subsample	465	1.023	51.9 (11.6)	13.4 (1.6)	*"How old were you when your periods started?"*
InCHIANTI	Invecchiare in Chianti, aging in the Chianti area	597	1.038	68.2 (15.5)	13.3 (1.5)	*"How old were you when you had your first menstrual period?"*
Indiana	Indiana University premenopausal Caucasian women peak BMD study	1497	1.01	33.3 (7.2)	12.6 (1.4)	*At what age did your periods begin? __Years old.*
NFBC	Northern Finland Birth Cohort 1966	2648	1.027	31.2 (0.4)	12.9 (1.3)	*"How old were you when you started menstruating"*
NHS - CGEMS	Nurses' Health Study	2270	1.034	56.8 (6.4)	12.5 (1.4)	*" At what age did your menstrual periods begin?"*
NHS - HU	Nurses' Health Study	3090	1.019	55.7 (6.7)	12.5 (1.4)	*" At what age did your menstrual periods begin?"*
NTR	Netherlands Twin Register	1051	1.01	44.6 (13.6)	13.2 (1.4)	*"How old were you when you had your first menstrual period?"*
QIMR	Queensland Institute of Medical Research	3528	1.029	birth year 1964.8 (19.0)	13.1 (1.3)	*"How old were you when you had your first menstrual period?"*
RS1	Rotterdam Study 1	3175	1.019	69.6 (9.3)	13.5 (1.6)	*"How old were you when you had your first menstrual period?"*
RS2	Rotterdam Study 2	1119	1.002	65.1 (8.4)	13.3 (1.6)	*"How old were you when you had your first menstrual period?"*
RS3	Rotterdam Study 3	1112	1.012	56.2 (6.1)	13.1 (1.6)	*"How old were you when you had your first menstrual period?"*
SAGE	Study of Addiction: Genetics and Environment	1291	1.001	38.4 (9.1)	12.8(1.6)	*"At what age did you have your first menstrual period?"*
SardiNIA	SardiNIA Study	2158	1.225	43.9 (17.2)	13.2 (1.6)	*"At what age did your menstrual periods begin?"*
TwinsUK	TwinsUK	2276	1.006	58.2 (12.7)	13.0 (1.6)	*"How old were you when you had your first menstrual period?"*
TwinsUKII	TwinsUKII	671	1.059	55.4 (14.6)	13.1 (1.6)	*"How old were you when you had your first menstrual period?"*
TwinsUKIII	TwinsUKIII	1016	0.999	62.4 (11.6)	12.9 (1.5)	*"How old were you when you had your first menstrual period?"*
WGHS	Women's Genome Health Study	22028	1.095	54.7 (7.1)	12.4 (1.4)	*"At what age did your menstrual periods begin?'' with response categories ''9 or younger; 10; 11; 12; 13; 14; 15; 16; 17 or older.''*
Overall		87802	1.173			

Supplementary Table 2: Information on genotyping arrays and QC criteria used in each of the Stage 1 discovery studies.

		Genotyping			Imputation and analysis	
Study	**Array**	**Callrate cut-off**	**MAF* cut-off**	**HWE cut-off****	**Imputation program**	**Analysis program**
AGES-Reykjavik	Illumina HumanHap 370K CNV	98%	0.01	1.0E-06	MACH	PLINK
Amish	Affymetrix 500K and 6.0	95%	0.01	1.0E-06	MACH	MMAP***
ARIC	Affymetrix 6.0	90%	0.01	1.0E-06	MACH	ProABEL
B58C-T1DGC	Illumina 550K	NA	0.01	NA	MACH	ProbABEL
B58C-WTCCC	Affymetrix 500K	NA	0.01	NA	IMPUTE	QUICKTEST
CoLaus	Affymetrix 500K	70%	0.01	1.0E-06	IMPUTE	in house Matlab code
deCODE	Illumina HumanHap 300K and 370K CNV	95%	0.01	1.0E-06	IMPUTE	Logistic regression using allele count as a covariate
DNBC	Illumina Human660W-Quad BeadChip	95%	0.01	1.0E-03	MACH	MACH2QTL
EGCUT	Illumina HumanHap 370K CNV	98%	0.01	1.0E-06	IMPUTE	SNPTEST
EPIC-obesity cases	Affymetrix GeneChip 500K	90%	0.01	1.0E-06	IMPUTE	SNPTEST
EPIC-obesity cohort	Affymetrix GeneChip 500K	90%	0.01	1.0E-06	IMPUTE	SNPTEST
ERF	Illumina 6K, 318K, 370K, Afyymetrix 250K	98%	0.01	1.0E-06	MACH	ProbABEL
FHS	Affymetrix 500K + Affymetrix 50K	97%	0.01	1.0E-06	MACH	R-packages
HBCS	Illumina HumanHap610 quad (modified)	95%	0.01	1.0E-06	MACH	ProbABEL
Health 2000 (Genmets) cases	Illumina HumanHap610 quad (modified)	95%	0.01	1.0E-06	MACH	ProbABEL
Health 2000 (Genmets) controls	Illumina HumanHap610 quad (modified)	95%	0.01	1.0E-06	MACH	ProbABEL
InCHIANTI	Illumina HumanHap 550K	98%	0.01	1.0E-04	IMPUTE	SNPTEST
Indiana	Illumina HumanHap 610 Quad version 1B	95%	0.01	1.0E-04	IMPUTE	MERLIN --fastassoc
NHS - CGEMS	Illumina HumanHap 550K	90%	0.01	NA	MACH	ProABEL
NHS - HU	Affymetrix 6.0	98%	0.01	1.0E-04	MACH	ProABEL
NFBC	Illumina Infinium 370CNV Duo	95%	0.01	1.0E-06	MACH	ProbABEL
NTR	Affymetrix 500K Perlegen	95%	0.01	1.0E-05	IMPUTE	SNPTEST
QIMR	Illumina Human610-Quadv1 and 370K CNV	95%	0.01	1.0E-05	MACH	MERLIN --fastassoc
RS1	Illumina HumanHap 550K	98%	0.01	1.0E-06	MACH	MACH2QTL
RS2	Illumina HumanHap 550K	98%	0.01	1.0E-06	MACH	MACH2QTL
RS3	Illumina HumanHap 550K	98%	0.01	1.0E-06	MACH	MACH2QTL
SAGE	Illumina Human 1Mv1_C	98%	0.01	1.0E-04	IMPUTE	SNPTEST
SardiNIA	Affymetrix 10K, 500K	90%	0.05	1.0E-06	MACH	MERLIN --fastassoc
TwinsUK	Illumina HumanHap 300K	95% (MAF 5%) / 99% (MAF 1-5%)	0.01	5.7E-05	IMPUTE	GenABEL
TwinsUKII	Illumina Hap610Quad	95% (MAF 5%) / 99% (MAF 1-5%)	0.01	5.7E-05	IMPUTE	GenABEL
TwinsUKIII	Illumina Hap610Quad	95% (MAF 5%) / 99% (MAF 1-5%)	0.01	5.7E-05	IMPUTE	GenABEL
WGHS	Illumina HumanHap300 Duo "+"	98%	0.01	1.0E-06	MACH	MACH2QTL

*Minor Allele Frequency

**Hardy-Weinburg equilibrium p-value cut-off

***Mixed model analysis for pedigrees

Supplementary Table 3: Results of conditional analyses to verify the presence of additional independent signals for age at menarche.

Supplementary Table 3. Results of conditional analyses to verify the presence of additional independent signals for age at menarche

Possible second signals from the stage 1 meta-analysis

Chr.	Position (B36)	SNP	Alleles[a]	Freq. modelled allele	Effect size (years/allele)	SE	*P*- value[b]	*P*- value[c 2-GC]
2	199561433	rs1947530	A/C	0.66	-0.047	0.008	2.34E-09	3.23E-08
14	99952158	rs10144321	A/G	0.75	0.048	0.008	9.93E-09	1.12E-07

Results from conditional analysis

Chr.	Position (B36)	SNP	Alleles[a]	Freq. coding allele	Effect size (years/allele)	SE	*P*- value[b]	*P*- value[c 2-GC]
2	199561433	rs1947530	A/C	0.66	-0.037	0.008	1.37E-06	8.04E-06
14	99952158	rs10144321	A/G	0.75	0.038	0.009	7.10E-06	3.28E-05

[a]modelled/nonmodelled allele

[b] P-value with genomic control applied to individual studies

[c] P-value with additional adjustment for overall genomic control

(B36) Position according to HapMap Build36

Conditional analyses were adjusted for the top SNP at the 42 genome-wide significant regions (in addition to birth year). Displayed results are based on meta-analysis of all 32 Stage 1 studies.

The possible second signals on chromosomes 2 and 14 failed to reach genome-wide significance in the conditional analyses.

Supplementary Table 4: Details of the 17 studies that contributed to replication for association with age at menarche.

Study	Description	Mean age (SD)	Mean Age at Menarche (SD)	N_SNPs	N women (max)
in silico replication					
BHS	Bogalusa Heart Study	15.8 (4.5)	12.4 (1.2)	42	343
EGCUT	Estonian Genome Center, University of Tartu	38.0 (15.9)	13.3 (1.4)	42	196
INGI - Carlantino	Italian Network of Genetic Isolates	48.1 (19.4)	12.9 (1.6)	42	322
INGI - Friuli Venezia Giulia	Italian Network of Genetic Isolates	50.6 (18.1)	13.2 (1.6)	42	338
INGI - Val Borbera	Italian Network of Genetic Isolates	54.4 (18.3)	12.9 (1.5)	42	910
KORA F3	Cooperative Health Research in the Region of Augsburg, KOoperative Gesundheitsforschung in der Region Augsburg	61.8 (10.1)	13.7 (1.5)	41	809
KORA S4	Cooperative Health Research in the Region of Augsburg, KOoperative Gesundheitsforschung in der Region Augsburg	53.5 (8.8)	13.5 (1.5)	42	898
SASBAC cases	Singapore and Swedish Breast Cancer Study	62.6 (6.3)	13.4 (1.4)	41	723
SASBAC controls	Singapore and Swedish Breast Cancer Study	62.6 (6.3)	13.5 (1.4)	40	685
SEARCH	Ovarian cancer cases	birth year 1942.7 (9.9)	12.8 (1.5)	42	1126
STR_MZ twins*	Swedish National Twin Cohort	65.3 (5.82)	13.7 (1.28)	41	151
Raine	Raine Study, Western Australia	14.1 (0.19)**	12.8 (1.13)	42	527
Orcades	Orkney Complex Disease Study, EUROpean Special Populations reseArch Network	52.7 (15.3)	12.8 (1.4)	42	348
SPLIT	Split, Croatia	46.7 (13.9)	13.5 (1.6)	42	283
KORCULA	Korcula Island, Croatia	54.8 (13.5)	13.5 (1.6)	42	508
VIS	Vis Island, Croatia (EUROSPAN)	56.2 (13.5)	13.5 (1.7)	42	502
de novo replication					
ALSPAC mothers	Avon Longitudinal Study of Parents and Children	28.2 (4.8)	12.8 (1.5)	30	6,118

*302 twin pairs with average age at menarche used

**Girls not reaching menarche by this exam were asked to return a slip of paper reporting the dates of their first two periods to the investigators

Supplementary Table 5: Meta-analysed results of replication studies (up to 14,731 women).

SNP	Nearest gene(s)	MAF[a]	Alleles[b]	N	Beta[c]	SE	*P*- value
Previous menarche loci							
rs7759938	*LIN28B*	0.32	C/T	14,185	6.3	1.0	4.6E-11
rs2090409	*TMEM38B*	0.31	A/C	14,708	-4.4	0.9	2.7E-06
30 novel menarche loci							
rs1079866	*INHBA*	0.15	G/C	14731	1.7	1.3	1.9E-01
rs466639	*RXRG*	0.13	T/C	14279	-2.9	1.3	3.1E-02
rs6438424	*3q13.32*	0.50	A/C	8634	-3.0	1.1	6.7E-03
rs1398217	*FUSSEL18*	0.43	G/C	14344	-2.7	0.9	2.3E-03
rs12617311	*PLCL1*	0.32	A/G	14007	-2.5	1.0	1.1E-02
rs9635759	*CA10*	0.32	A/G	14002	2.6	1.0	1.1E-02
rs6589964	*BSX*	0.48	A/C	13754	-1.6	0.9	8.3E-02
rs10980926	*ZNF483*	0.36	A/G	14227	0.8	0.9	3.8E-01
rs17268785	*CCDC85A*	0.17	G/A	14233	2.9	1.2	1.5E-02
rs13187289	*PHF15*	0.20	G/C	14303	2.8	1.2	1.4E-02
rs7642134	*VGLL3*	0.38	A/G	14205	-2.8	0.9	2.1E-03
rs17188434	*NR4A2*	0.07	C/T	14356	-2.2	1.8	2.2E-01
rs2002675	*TRA2B, ETV5*	0.42	G/A	14334	2.5	0.9	6.6E-03
rs7821178	*PXMP3*	0.34	A/C	14151	-1.7	0.9	8.0E-02
rs1659127	*MKL2*	0.34	A/G	14021	2.2	1.0	2.5E-02
rs10423674	*CRTC1*	0.35	A/C	13543	1.6	1.0	1.1E-01
rs10899489	*GAB2*	0.15	A/C	14201	1.4	1.2	2.5E-01
rs6575793	*BEGAIN*	0.42	C/T	13899	0.7	1.0	4.6E-01
rs4929923	*TRIM66*	0.36	T/C	8510	2.9	1.2	1.6E-02
rs6439371	*TMEM108, NPHP3*	0.34	G/A	8581	2.6	1.2	3.0E-02
rs900145	*ARNTL*	0.30	C/T	8649	2.3	1.2	6.5E-02
rs6762477	*RBM6*	0.44	G/A	12447	1.4	1.0	1.5E-01
rs2947411	*TMEM18*	0.17	A/G	8657	3.4	1.4	1.9E-02
rs1361108	*C6orf173, TRMT11*	0.46	T/C	14126	-1.7	0.9	6.0E-02
rs1364063	*NFAT5*	0.43	C/T	8669	3.0	1.1	7.1E-03
rs633715	*SEC16B*	0.20	C/T	14274	-1.5	1.1	1.9E-01
rs4840086	*PRDM13, MCHR2*	0.42	G/A	8669	-2.0	1.1	7.5E-02
rs7617480	*KLHDC8B*	0.22	A/C	14341	1.2	1.0	2.4E-01
rs9939609	*FTO*	0.40	A/T	8665	0.7	1.2	5.3E-01
rs852069	*PCSK2*	0.37	A/G	14306	-0.9	0.9	3.3E-01
10 possible menarche loci							
rs757647	*KDM3B*	0.22	A/G	14326	-0.8	1.1	4.4E-01
rs9555810	*C13orf16, ARHGEF7*	0.28	G/C	14266	0.7	1.0	4.9E-01
rs16938437	*PHF21A*	0.09	T/C	14330	-1.4	1.6	3.8E-01
rs2687729	*EEFSEC*	0.27	G/A	8669	1.3	1.3	3.2E-01
rs1862471	*OLFM2*	0.47	G/C	13470	-0.1	1.0	9.4E-01
rs12472911	*LRP1B*	0.20	C/T	8585	2.1	1.4	1.4E-01
rs3914188	*ECE2*	0.27	G/C	14085	-0.3	1.0	7.9E-01
rs2243803	*SLC14A2*	0.40	A/T	8659	1.0	1.1	3.9E-01
rs3743266	*RORA*	0.32	C/T	8666	-0.3	1.2	7.8E-01
rs7359257	*IQCH*	0.45	A/C	14303	-0.5	0.9	6.0E-01

[a] Minor allele frequency

[b] Minor / Major allele

[c] Per allele change in age at menarche (weeks)

Supplementary Table 6: Variance in age at menarche explained by the 42 known, confirmed and possible novel loci in each of the 17 replication studies.

Study	Description	N women in full model	N_SNPs	Variance Explained (r2)
in silico replication				
SEARCH	Ovarian cancer cases	1126	42	0.036
INGI - Val Borbera	Italian Network of Genetic Isolates	910	42	0.061
KORA S4	Cooperative Health Research in the Region of Augsburg, KOoperative Gesundheitsforschung in der Region Augsburg	898	42	0.054
KORA F3	Cooperative Health Research in the Region of Augsburg, KOoperative Gesundheitsforschung in der Region Augsburg	805	41	0.058
KORCULA	Korcula Island, Croatia (EUROSPAN)	508	41	0.077
VIS	Vis Island, Croatia (EUROSPAN)	502	42	0.150
Orcades (Eurospan)	Orkney Complex Disease Study, EUROpean Special Populations reseArch Network (EUROSPAN)	348	40	0.110
BHS	Bogalusa Heart Study	338	42	0.099
INGI - Friuli Venezia Giulia	Italian Network of Genetic Isolates	338	42	0.151
INGI - Carlantino	Italian Network of Genetic Isolates	322	42	0.181
SPLIT	Split, Croatia	283	42	0.163
EGCUT	Estonian Genome Center, University of Tartu	196	42	0.186
SASBAC controls	Singapore and Swedish Breast Cancer Study	188	42	0.238
SASBAC cases	Singapore and Swedish Breast Cancer Study	158	41	0.256
STR_MZ twins	Swedish National Twin Cohort	151	42	0.158
Raine	Raine Study, Western Australia	88	42	0.454
de novo replication				
ALSPAC mothers	Avon Longitudinal Study of Parents and Children	3938	30	0.011

Sorted by sample size. The largest four in silico replication studies are highlighted as giving rise to more reliable estimates.

Supplementary Table 7: Biological functions of genes at/near the 42 known, confirmed or possible novel menarche loci.

SNP	Nearest gene(s)	Distance from gene (kb)	Chr	Gene name & function
Previous menarche loci				
rs7759938	*LIN28B*	~26kb	6	**lin-28 homolog B (C. elegans).** Also associated with short adult height. Regulates let-7 micro-RNA processing. Deletarious mutations in lin-28 in C.
rs2090409	*TMEM38B*	~400kb	9	**transmembrane protein 38B.** Trimeric intracellular cation channel type B.
30 novel menarche loci				
rs1079866	*INHBA*	~250kb	7	**inhibin, beta A.** Joins the alpha subunit to form an inhibitor of pituitary secretion of follicle stimulating hormone (FSH). Circulating levels of inhibin A rise with gonadal growth during puberty and negatively feedback on the pituitary.
rs466639	*RXRG*	intronic	1	**retinoid X receptor, gamma.** A nuclear receptor which forms dimers with the receptors for retinoic acid, thyroid hormone, and vitamin D, increasing both DNA binding and transcriptional function on their respective response elements.
rs6438424	*3q13.32*	*intergenic*	3	
rs1398217	*FUSSEL18*	intronic	18	**functional smad suppressing element 18.** Specifically neuronally-expressed member of a family of nuclear oncoproteins that repress transforming growth factor-beta (TGF-beta) signaling through inhibition of transcriptional activity of Smad proteins.
rs12617311	*PLCL1*	~195kb	2	**phospholipase c-like 1.** Involved in an inositol phospholipid-based intracellular signaling cascade.
rs9635759	*CA10*	~94kb	17	**carbonic anhydrase X.** Encodes a protein with likely no carbonic anhydrase catalytic activity, but is expressed widely in the central nervous system.
rs6589964	*BSX*	~18kb	11	**brain specific homebox.** A DNA binding protein and transcriptional activator. In the mouse Bsx is expressed specifically in the pineal gland, telencephalic septum, hypothalamic pre-mammillary body and arcuate nucleus, and is necessary for postnatal growth.
rs10980926	*ZNF483*	intronic	9	**zinc finger protein 483.** Unknown function. Is conserved in chimpanzee, dog, mouse, and rat.
rs17268785	*CCDC85A*	intronic	2	**coiled-coil domain containing 85A.** Unknown function.
rs13187289	*PHF15*	~12kb	5	**PHD finger protein 15.** Encodes a PHD zinc finger protein transcription factor. Has been reported to be downregulated in human peripheral blood mononuclear cells by melatonin.
rs7642134	*VGLL3*	~70kb	3	**vestigial like 3 (Drosophila).** A transcriptional regulator with a possible role in the suppression of ovarian tumorigenesis.
rs17188434	*NR4A2*	~84kb	2	**nuclear receptor subfamily 4, group A, member 2.** Encodes a transcription factor essential for the differentiation of dopaminergic neurons in substantia nigra. Mutations are associated with disorders of dopaminergic dysfunction, including Parkinsons disease.
rs2002675	*TRA2B; ETV5*	~4kb, ~135kb	3	**transformer 2 beta homolog (Drosophila).** Related to the ancestral gene in Drosophila, Transformer-2 (Tra2), which encodes an RNA-binding protein, an important regulator of sex determination. **ets variant 5.** A member of the ets family of transcription factors.
rs7821178	*PXMP3*	~181kb	8	**peroxisomal membrane protein 3.** Encodes an integral peroxisomal membrane protein required for peroxisome biogenesis. Mutations result in the peroxisomal biogenesis disorders Zellweger syndrome and infantile Refsum disease.
rs1659127	*MKL2*	~28kb	16	**MKL/myocardin-like 2**. A broadly expressed member of a family of transcriptional coactivators which bind to serum response factor (SRF) and strongly activate transcription from promoters with SRF binding sites.
rs10423674	*CRTC1*	intronic	19	**CREB regulated transcription coactivator 1.** Encodes an activator of cellular gene expression. Crtc1(-/-) mice are hyperphagic, obese and infertile, and females have low circulating luteinizing hormone levels. Leptin potentiates the effects of Crtc1 transcriptional activity, and Crtc1 over-expression in hypothalamic cells increases Kiss1 gene expression.
rs10899489	*GAB2*	intronic	11	**GRB2-associated binding protein 2.** Encodes the principal activator of phosphatidylinositol-3 kinase in response to activation of the high affinity IgE receptor. Forms a complex with growth factor receptor-bound protein 2 (Grb2) involved in signal transduction/cell communication. Has been associated with Alzheimer's disease and implicated in angiogenesis and melanoma tumor progression and metastasis.
rs6575793	*BEGAIN*	intronic	14	**brain-enriched guanylate kinase-associated homolog (rat).** Lies in the Dlk1 / Gtl2 imprinting region and shows transcript-specific genomic imprinting in the mouse (preferential paternal transcription).
rs4929923	*TRIM66*	3'UTR	11	**tripartite motif-containing 66.** Encodes TIF1delta, one of the Transcriptional intermediary factor 1 (TIF1) proteins which are encoded by a family of highly conserved developmental and physiological control genes. These proteins have been implicated in epigenetic mechanisms of transcriptional repression. Uniquely, TRIM66 expression is confined to haploid elongating spermatids.
rs6439371	*TMEM108; NPHP3*	~146kb, ~170kb	3	**transmembrane protein 108**. Unknown function. **nephronophthisis 3 (adolescent)**. Possible role in renal tubular development and function.
rs900145	*ARNTL*	~5 kb	11	**aryl hydrocarbon receptor nuclear translocator-like** (Also known as *BMAL1*). The encoded protein forms a complex with CLOCK to activate PER1 and possibly other circadian rhythm-associated genes. Expression in the ovary is elevated following the LH surge. *Bmal1* null mice lack central and peripheral cellular rhythms and have delayed puberty.
rs6762477	*RBM6*	intronic	3	**RNA binding motif protein 6.** An RNA binding protein which potentially modulates apoptosis and has been implicated in myeloid proliferative disease.
rs2947411	*TMEM18*	~53kb	2	**transmembrane protein 18.** Modulates the migration of neural stem cells.
rs1361108	*C6orf173; TRMT11*	~98kb, ~407kb	6	**chromosome 6 open reading frame 173**. Is commonly up-regulated in many human cancer tissues and possesses transforming activities in mouse fibroblast cell line. **tRNA methyltransferase 11 homolog (S. cerevisiae)**. Putative member of the RNA methylase enzyme family.
rs1364063	*NFAT5*	~10kb	16	**nuclear factor of activated T-cells 5, tonicity-responsive**. Encodes a member of the nuclear factors of activated T cells family of transcription factors, which regulate the inducible gene transcription during the immune response.
rs633715	*SEC16B*	~44kb	1	**SEC16 homolog B (S. cerevisiae).** Homolog of an ancestral gene that is required for the organization of transitional endoplasmic reticulum (ER) sites and protein export.
rs4840086	*PRDM13, MCHR2*	~145kb, ~160kb	6	**PR domain containing 13.** Regulation of transcription. **melanin concentrating hormone receptor 2.** This orphan G protein-coupled receptor shows high affinity binding to the neuropeptide melanin-concentrating hormone (MCH), which is known to regulate energy homeostasis and mood via MCHR1.
rs7617480	*KLHDC8B*	intronic	3	**lysine (K)-specific demethylase 3B.** Is a candidate tumor suppressor gene based on its predicted function, a regulator of chromatin remodeling, and
rs9939609	*FTO*	intronic	16	**fat mass and obesity associated.** Involved in nucleic acid demethylation, but exact function is unknown. Is transcriptionally regulated by feeding and fasting.
rs852069	*PCSK2*	~84kb	20	**proprotein convertase subtilisin/kexin type 2.** Cleaves latent precursor proteins, such as proinsulin and proopiomelanocortin, into their biologically active products. PCSK2 differs from PCSK1 in that it additionally cleaves proluteinizing-hormone-releasing hormone.
10 possible menarche loci[j]				
rs757647	*KDM3B*	intronic	5	**lysine (K)-specific demethylase 3B.** Is a candidate tumor suppressor gene based on its predicted function, a regulator of chromatin remodeling, and clonogenic growth suppressive activities.
rs9555810	*C13orf16, ARHGEF7*	~185kb, ~223kb	13	**chromosome 13 open reading frame 16.** Uncharacterised protein. **Rho guanine nucleotide exchange factor (GEF) 7**. Belongs to a family of cytoplasmic proteins that activate Rho proteins by exchanging bound GDP for GTP. ARHGEF7 has a role in cell proliferation through phosphorylation of FOXO3a. FOXO3a knockout mice are infertile due to early depletion of the follicle pool. Patients with microdeletions of 13q33-34 have mental retardation and microcephaly, and male patients frequently have genital malformations.
rs16938437	*PHF21A*	intronic	11	**PHD finger protein 21A.** A component of the BRAF-HDAC complex (BHC), PHF21A modulates the repression of neurosecretion through the transcription repressor element-1 silencing transcription factor (REST). Possible role in spermatogenesis.
rs2687729	*EEFSEC*	intronic	3	**eukaryotic elongation factor, selenocysteine-tRNA-specific**. Regulates selenocysteine incorporation into mRNAs in the generation of selenoproteins.
rs1862471	*OLFM2*	intronic	19	**olfactomedin 2.** Is one of a diverse family of olfactomedins, which are secreted glycoproteins that have been implicated in the timing and growth of the neural crest, and include the glaucoma-associated protein myocilin.
rs12472911	*LRP1B*	intronic	2	**low density lipoprotein-related protein 1B.** Belongs to the low density lipoprotein (LDL) receptor gene family, which have a wide variety of roles in normal cell function and development. LRP1B has been implicated in tumorigenesis and associated with ageing.
rs3914188	*ECE2*	3'UTR	3	**endothelin converting enzyme 2.** A type II metalloprotease that generate functionally pleiotropic members of the endothelin vasoactive peptide family. Downregulated in Alzheimer's disease.
rs2243803	*SLC14A2*	~238kb	18	**solute carrier family 14 (urea transporter), member 2 (SLC14A2)**. Encodes the renal tubular transporter of urea.
rs3743266	*RORA*	3'UTR	15	**RAR-related orphan receptor A.** Encodes the retinoid-related orphan receptor, RORalpha, a nuclear hormone receptor critical for the development of the cerebellum. May play a role in maturation of photoreceptors and regulation of the circadian clock.
rs7359257	*IQCH*	intronic	15	**IQ motif containing H.** Unknown function.

Supplementary Table 8: Functional networks and their relevant functions for 42 candidate genes associated with age at menarche.

	Age at menarche associated genes in Network	Other related genes/molecules in network	Associated network functions
Network 1: $p=1x10^{-37}$	16 genes: ARHGEF7, CRTC1, ECE2, ETV5, INHBA, KLHDC8B, MKL2, NFAT5, OLFM2, PHF15, PHF21A, PLCL1, RBM6, SEC16B, SLC14A2, TRA2B	AR, CRYAB, E2F1, FABP4, HNF4A, INHBC, INHBE, MIR292, MIR136 (includes EG:406927), MIRLET7B (includes EG:406884), MYC, NBAS, NCOA3, PCK1, RARG, RXRB, SNAP25, ST13, YWHAG	Gene Expression, Cellular Growth and Proliferation, Cellular Function and Maintenance
Network 2: $p=1x\ 10^{-23}$	11 genes: ARNTL, BEGAIN, CCDC85A, GAB2, LRP1B, MCHR2, NR4A2, PCSK2, PXMP3, RORA, RXRG	ACADM, Acox, ACSL1, BGLAP, CYP24A1, CYP4A11, DLG4, EHHADH, FABP, FABP1, FABP3, FABP5, HMG CoA synthase, ITGB3BP, LIVTR, MIR24-1 (includes EG:407012), MMP11, PMCH, RBP2, RQCD1, RXRA, SRC, TLE1, ZFP64	Lipid Metabolism, Small Molecule Biochemistry, Molecular Transport

		p-value	***# focus genes***
Diseases and disorders	Genetic disorder	1.0E-03 - 3.5E-02	24
	Neurological disease	1.0E-03 - 2.7E-02	17
	Psychological disorders	1.0E-03 - 7.0E-03	10
	Endocrine system disorders	1.4E-03 - 1.6E-02	13
	Metabolic disease	1.4E-03 - 1.6E-02	14
Molecular and cellular functions	Gene expression	1.5E-05 - 4.4E-02	14
	Small molecule biochemistry	1.4E-04 - 4.8E-02	7
	Cellular development	5.1E-04 - 4.8E-02	8
	Cellular growth and proliferation	5.1E-04 - 4.8E-02	7
	Antigen presentation	2.3E-03 - 2.3E-03	1

Ingenuity Pathway Analysis (IPA) Knowledge Base 8.5 (Ingenuity Systems, CA, USA) was used to explore the functional relationship between proteins encoded by the genes or nearest genes of the 42 genome-wide significant loci. The genes were entered into the Ingenuity database and analyzed for direct interactions only. Networks were generated with a maximum size of 35 genes.

Supplementary Table 9: Pathways significantly associated with age at menarche identified by GSEA.

			95th percentile enrichment cutoff				75th percentile enrichment cutoff				
Database	**Gene set**	**# genes in category tested by GSEA**	**Nominal GSEA P-value**	**FDR corrected P-value**	**Observed # genes above cutoff**	**Expected # genes above cutoff**	**Nominal GSEA P-value**	**FDR corrected P-value**	**Observed # genes above cutoff**	**Expected # genes above cutoff**	**Genes nearest to validated age at menarche SNPs**
Panther	Coenzyme A biosynthesis	7	2.0E-04	4.9E-03	4	0	1.2E-02	1.4E-01	5	2	
Panther	Angiotensin II stimulated signaling through G proteins and beta-arrestin	5	6.0E-04	6.2E-03	3	0	1.0E-01	3.9E-01	3	1	
PANTHER BIOLOGICAL PROCESS	Stress response	172	4.7E-02	9.0E-01	14	9	3.7E-05	5.1E-03	67	43	NR4A2, NFAT5
PANTHER BIOLOGICAL PROCESS	Coenzyme metabolism	52	7.0E-04	1.5E-01	9	3	3.0E-04	1.9E-02	25	13	
PANTHER BIOLOGICAL PROCESS	General mRNA transcription activities	39	5.9E-01	8.9E-01	2	2	4.0E-04	4.4E-02	19	10	

MAGENTA (Ref 44) was used to test for enrichment of multiple modest associations with age at menarche in 2529 pathways from Gene Ontology, PANTHER, KEGG and Ingenuity.
Only gene sets with FDR<0.05 are presented here. GSEA P-values in bold refer to P-values that pass the Bonferroni correction cutoff (accounting for testing two enrichment cutoffs).

Supplementary Table 10: The 42 known, confirmed or possible novel menarche loci related to lymphoblastoid cell line (LCL) eQTLs.

Nearest gene(s)	SNP	chr	position	Gene Expressed	Mechanism	P-value
LIN28B	rs7759938	6	105485647	-	-	-
TMEM38B	rs2090409	9	108006909	-	-	-
INHBA	rs1079866	7	41436618	-	-	-
RXRG	rs466639	1	163661506	*TEX12*	Trans (Chr 11)	2x10-7
3q13.32	rs6438424	3	119057512	-	-	-
BSX	rs6589964	11	122375893	-	-	-
CA10	rs9635759	17	46968784	-	-	-
ZNF483	rs10980926	9	113333455	-	-	-
PLCL1	rs12617311	2	199340810	-	-	-
FUSSEL18	rs1398217	18	43006236	-	-	-
FTO	rs9939609	16	52378028	-	-	-
NR4A2	rs17188434	2	156805022	-	-	-
CCDC85A	rs17268785	2	56445587	-	-	-
BEGAIN	rs6575793	14	100101970	-	-	-
PHF15	rs13187289	5	133877076	-	-	-
GAB2, ZNF75C	rs10899489	11	77773021	*GAB2*	Cis	3x10-7
OLFM2	rs1862471	19	9861322	-	-	-
C13orf16, ARHGEF7	rs9555810	13	110979438	-	-	-
PXMP3	rs7821178	8	78256392	-	-	-
CRTC1	rs10423674	19	18678903	-	-	-
PCSK2	rs852069	20	17070593	-	-	-
KDM3B	rs757647	5	137735214	*ATP6V1H*	Trans (Chr 8)	6x10-7
PHF21A	rs16938437	11	46009151	-	-	-
RBM6	rs6762477	3	50068213	*RBM6*	Cis	4.8x10-11
SEC16B	rs633715	1	176119203	-	-	-
KLHDC8B	rs7617480	3	49185736	-	-	-
VGLL3	rs7642134	3	86999572	-	-	-
ECE2	rs3914188	3	185492742	-	-	-
C6orf173, TRMT11	rs1361108	6	126809293	-	-	-
MKL2	rs1659127	16	14295806	-	-	-
TRA2B, ETV5	rs2002675	3	187112262	-	-	-
IQCH	rs7359257	15	65489961	-	-	-
ARNTL	rs900145	11	13250481	-	-	-
PRDM13, MCHR2	rs4840086	6	100315159	-	-	-
EEFSEC	rs2687729	3	129377916	-	-	-
TMEM108, NPHP3	rs6439371	3	134093442	-	-	-
TMEM18	rs2947411	2	604168	-	-	-
TRIM66	rs4929923	11	8595776	-	-	-
RORA	rs3743266	15	58568805	*NARG2*	Cis	7x10-7
SLC14A2	rs2243803	18	41210670	-	-	-
LRP1B	rs12472911	2	141944979	-	-	-
NFAT5	rs1364063	16	68146073	-	-	-

Using publicly available LCL dataset (http://www.sph.umich.edu/csg/liang/asthma/ mRNA by SNP Browser) from Dixon et al, Nature Genetics 2007. Only P-values <1.0E7 are shown.

Supplementary Table 11: Adipose tissue eSNPs related to age at menarche.

eSNP	Chr	Position	Menarche P-value	eSNP P-value	Transcript	Closest gene	Distance	Allele 1	Allele 2	Allele 1 frequency
rs4660740	1	43921204	4.6E-05	1.2E-06	MED8	*JMJD2A*	22571	a	g	0.744
rs823096	1	203946510	8.9E-05	1.5E-08	PM20D	*NUCKS1*	7221	t	g	0.439
rs823114	1	203986155	1.2E-04	8.0E-13	PM20D	*NUCKS1*	239	a	g	0.540
rs1378410	2	199182802	1.2E-04	4.4E-05	MARS2	*PLCL1*	461509	a	g	0.248
rs4955439	3	49220649	**2.8E-08**	2.5E-14	WDR6	*CCDC36*	9785	t	g	0.262
rs4955417	3	49273209	**5.5E-08**	7.3E-09	WDR6	*CCDC36*	3050	t	c	0.262
rs2236950	3	50395558	2.2E-05	8.9E-16	HYAL3	*CACNA2D2*	20323	a	c	0.184
rs9310074	3	88227760	2.4E-06	5.6E-05	ZNF654	*CGGBP1*	36924	t	c	0.843
rs4687889	3	119020129	**1.6E-11**	1.3E-04	AK022000	*IGSF11*	1082041	t	c	0.532
rs10512868	3	134067262	1.9E-05	3.5E-06	NPHP3	*NPHP3*	143296	a	g	0.173
rs4912539	3	185544081	4.1E-06	6.8E-05	EIF2B5	*FAM131A*	2675	a	g	0.700
rs4698894	4	104540550	1.2E-05	3.9E-08	CISD2	*TACR3*	189523	a	g	0.760
rs329319	5	133934508	3.6E-05	3.8E-05	PITX1	*PHF15*	12309	a	g	0.428
rs2524044	6	31364732	7.9E-06	1.6E-06	HCG18	*HLA-C*	16898	t	g	0.834
rs222461	6	52997234	1.8E-04	6.3E-09	FBXO9	*ICK*	23178	a	c	0.752
rs11188661	10	97950983	1.2E-04	1.6E-07	AK000974	*BLNK*	9531	a	g	0.314
rs10501087	11	27626684	1.2E-04	1.4E-04	LIN7C	*BDNF*	6333	t	c	0.798
rs10835211	11	27657941	9.4E-06	9.2E-12	LIN7C	*BDNF*	19815	a	g	0.252
rs4944196	11	77686379	**8.3E-09**	9.3E-05	C11orf67	*GAB2*	44195	a	g	0.160
rs7160413	14	100185286	2.1E-05	1.5E-04	C14orf134	*DLK1*	77719	a	g	0.079
rs4782294	16	19774522	8.0E-05	2.0E-06	GPRC5B	*IQCK*	1836	t	c	0.128
rs1398883	17	39115918	1.5E-04	2.0E-04	KRTHA8	*MEOX1*	21130	a	g	0.408
rs2836961	21	39548890	8.1E-06	4.0E-07	WRB	*BRWD1*	41345	a	c	0.612

Menarche P-values are derived from our Stage 1 meta-analysis of 32 studies

All 23 eSNPs were significantly associated with age at menarche after correction for multiple testing (1/n threshold for 5,184 independent tests was P<1.93 x 10-4).

eSNP P-values are derived from the Icelandic Family Adipose cohort (Ref 26)

Supplementary Table 12: Age at menarche associations for 8,770 SNPs in 16 candidate genes and their surrounding regions (+/-300kb).

See Excel file online.

Supplementary Table 13: Associations between known obesity-related SNPs and age at menarche.

Nearby Gene	SNP*	Chr	Obesity Phenotype	Menarche Beta (weeks/allele)	Menarche SE	Menarche *P* value	Obesity-susceptibility allele	Menarche-decreasing allele
FTO	rs9939609	16q12	BMI	2.5	0.4	**3.3E-11**	A	A
SEC16B	rs10913469	1q25	BMI	2.6	0.5	**2.4E-08**	C	C
GNPDA2	rs10938397	4p13	BMI	2.1	0.4	**8.7E-08**	G	G
NEGR1	rs2815752	1p31	BMI	1.9	0.4	**5.9E-07**	A	A
TMEM18	rs6548238	2p25	BMI	2.7	0.5	**7.1E-07**	C	C
FAIM2	rs7138803	12q13	BMI	1.8	0.4	**1.7E-06**	A	A
BDNF	rs4923461	11p14	BMI	1.7	0.5	**3.1E-04**	A	A
KCTD15	rs11084753	19q13	BMI	1.4	0.4	**5.9E-04**	G	G
TRA2B, ETV5	rs7647305	3q27	BMI	1.2	0.5	**9.0E-03**	C	C
MTCH2	rs10838738	11p11	BMI	0.6	0.4	1.4E-01	G	G
MC4R	rs17782313	18q21	BMI	0.6	0.4	1.5E-01	C	T
SH2B1	rs7498665	16p11	BMI	0.2	0.4	5.7E-01	G	G
TFAP2B	rs987237	6p12	WHR	1.6	0.5	**7.8E-04**	G	G
MSRA	rs7826222	8p23	WHR	1.8	0.8	**2.4E-02**	G	G
NRXN3	rs10146997	14q31	WHR	0.7	0.5	1.4E-01	G	G
LYPLAL1	rs2605100	1q41	WHR	0.3	0.4	4.6E-01	G	G
NPC1	rs1805081	18q11	Obesity	0.7	0.4	5.1E-02	T	T
PTER	rs10508503	10p12	Obesity	1.1	0.7	1.0E-01	C	T
MAF	rs1424233	16q23	Obesity	0.1	0.4	8.3E-01	T	C

WHR: waist-hip ratio

Menarche P-values are derived from our Stage 1 meta-analysis of 32 studies with genomic control applied to individual studies.

*Selected SNPs at each locus are those published for association with BMI/WHR/obesity (rather than those with the strongest signal for age at menarche)

Supplementary Table 14: Associations between known height SNPs and age at menarche.

Gene	SNP*	Chr	Position	Menarche Beta (weeks/allele)	Menarche SE	Menarche *P* value	Height-increasing allele	Menarche-increasing allele
LIN28B	rs314277	6	105514355	6.9	0.6	**2.1E-35**	a	a
PXMP3	rs7846385	8	78322734	2.5	0.4	**1.9E-09**	***c***	***t***
C6orf173	rs4549631	6	127008001	1.8	0.4	**4.9E-07**	***c***	***t***
SCMH1	rs6686842	1	41303458	-1.1	0.4	**3.3E-03**	***t***	***c***
Histone cluster 1	rs10946808	6	26341366	1.1	0.4	**6.4E-03**	a	a
NOG	rs4794665	17	52205328	-0.9	0.4	**1.1E-02**	***a***	***g***
HMGA2	rs1042725	12	64644614	-0.8	0.4	**2.0E-02**	c	c
TBX2	rs757608	17	56852059	-0.9	0.4	**2.2E-02**	***a***	***g***
HLA Class III	rs2844479	6	31680935	-0.9	0.4	**2.4E-02**	***a***	***c***
ZBTB38	rs6440003	3	142576899	0.8	0.4	**3.5E-02**	a	a
CABLES1	rs4800148	18	18978326	-1.0	0.5	**3.7E-02**	***a***	***g***
ZNF462	rs4743034	9	108672174	0.8	0.4	6.4E-02	a	a
PPARD	rs2814993	6	34726871	0.9	0.5	7.2E-02	a	a
PPARD	rs4713858	6	35510763	-0.9	0.5	8.7E-02	g	g
CDK6	rs2282978	7	92102346	-0.6	0.4	1.3E-01	c	c
Histone cluster 2	rs11205277	1	148159496	0.6	0.4	1.4E-01	g	a
PTCH1	rs10512248	9	97299524	-0.6	0.4	1.5E-01	g	g
SPAG17	rs12735613	1	118685496	0.6	0.4	2.0E-01	g	a
HLA Class III	rs185819	6	32158045	-0.5	0.4	2.0E-01	t	c
HMGA1	rs1776897	6	34302989	1.2	0.9	2.0E-01	g	t
DYM	rs8099594	18	45245158	0.5	0.4	2.5E-01	a	a
RNF135	rs3760318	17	26271841	0.4	0.4	2.6E-01	g	a
NCAPG	rs16896068	4	17553938	-0.6	0.5	2.8E-01	g	g
DLEU7	rs3116602	13	50009356	-0.5	0.5	3.0E-01	t	g
GPR126	rs4896582	6	142745570	-0.4	0.4	3.0E-01	g	g
HHIP	rs1812175	4	145794294	-0.5	0.5	3.1E-01	g	g
TSEN15	rs2274432	1	182287568	-0.4	0.4	3.2E-01	a	g
FBLN5	rs8007661	14	91529711	0.4	0.5	4.4E-01	c	t
ANAPC13	rs10935120	3	135715782	-0.3	0.4	4.6E-01	g	g
BMP6	rs12198986	6	7665058	0.3	0.4	4.9E-01	a	a
GDF5	rs6060369	20	33370575	0.2	0.4	5.4E-01	c	t
ADAMSTSL3	rs2562784	15	82077496	0.3	0.5	5.6E-01	g	a
DOT1L	rs12986413	19	2121954	-0.2	0.4	6.2E-01	t	t
PLAG1	rs10958476	8	57258362	-0.2	0.5	6.9E-01	c	c
ADAMSTS17	rs4533267	15	98603794	-0.2	0.4	7.0E-01	a	g
EFEMP1	rs3791679	2	55950396	0.2	0.4	7.3E-01	a	a
ZNF678	rs1390401	1	225864573	0.2	0.5	7.5E-01	a	a
DNM3	rs678962	1	170456512	0.1	0.5	7.5E-01	g	t
SOCS2	rs11107116	12	92502635	0.1	0.4	7.6E-01	t	t
PLAG1	rs9650315	8	57318152	-0.2	0.6	7.9E-01	g	g
BMP2	rs967417	20	6568893	0.1	0.4	8.4E-01	g	a
GNA12	rs798544	7	2729628	-0.1	0.4	8.5E-01	c	c
IHH	rs6724465	2	219652090	-0.1	0.6	9.3E-01	g	g
ACAN	rs8041863	15	87160693	0.0	0.4	9.7E-01	a	a

Chi-square =7.02, P=0.008 for 11/44 SNPs associated with age at menarche (at P<0.05) vs. 2.2 expected by chance

However 7 height-increasing SNPs are associated with earlier menarche, and 4 with later menarche.

Menarche P-values are derived from our Stage 1 meta-analysis of 32 studies with genomic control applied to individual studies

Supplementary Table 15: Association of menarche loci with BMI in up to 32,530 adults in the GIANT consortium.

								Association with menarche				Association with BMI		
SNP	Nearest gene(s)	Distance from gene (kb)	Chr	Position (B36)	MAF	Minor allele	Major allele	Menarche decreasing allele	Beta (weeks/allele)	se	P-value	BMI increasing allele	P-value	Direction consistent[a]
rs9939609	FTO	intronic	16	52378028	0.40	A	T	A	2.12	0.39	3.1E-08	A	6.3E-17	y
rs2947411	TMEM18	~53kb	2	604168	0.17	A	G	G	2.84	0.51	1.7E-08	G	3.0E-05	y
rs4929923	TRIM66	3'UTR	11	8595776	0.36	T	C	C	2.27	0.40	1.2E-08	C	2.3E-03	y
rs3914188	ECE2	3'UTR	3	185492742	0.27	G	C	G	2.21	0.43	2.6E-07	G	5.6E-03	y
rs633715	SEC16B	~44kb	1	176119203	0.20	C	T	C	2.63	0.47	2.1E-08	C	6.8E-03	y
rs10899489	GAB2	intronic	11	77773021	0.15	A	C	C	3.09	0.54	8.1E-09	C	1.0E-02	y
rs466639	RXRG	intronic	1	163661506	0.13	T	C	T	4.20	0.57	1.3E-13	T	1.1E-02	y
rs13187289	PHF15	~12kb	5	133877076	0.20	G	C	C	3.02	0.48	1.9E-10	C	2.2E-02	y
rs7359257	IQCH	intronic	15	65489961	0.45	A	C	C	1.73	0.36	1.9E-06	C	2.9E-02	y
rs17268785	CCDC85A	intronic	2	56445587	0.17	G	A	A	3.22	0.50	9.7E-11	G	9.3E-02	n
rs9635759	CA10	~94kb	17	46968784	0.32	A	G	G	2.97	0.41	7.3E-13	G	1.0E-01	y
rs9555810	C13orf16, ARHGEF7	~185kb, ~223kb	13	110979438	0.28	G	C	C	2.31	0.43	5.6E-08	C	1.1E-01	y
rs1862471	OLFM2	intronic	19	9861322	0.47	G	C	C	2.03	0.39	1.5E-07	C	1.3E-01	y
rs2090409	TMEM38B	~400kb	9	108006909	0.31	A	C	A	4.73	0.39	2.2E-33	A	1.6E-01	y
rs757647	KDM3B	intronic	5	137735214	0.22	A	G	A	2.40	0.44	5.4E-08	A	1.7E-01	y
rs1398217	FUSSEL18	intronic	18	43006236	0.43	G	C	G	2.69	0.37	2.3E-13	C	2.2E-01	n
rs6439371	TMEM108, NPHP3	~146kb, ~170kb	3	134093442	0.34	G	A	A	2.32	0.41	1.3E-08	G	2.3E-01	n
rs12617311	PLCL1	~195kb	2	199340810	0.32	A	G	A	3.03	0.42	6.0E-13	G	2.3E-01	n
rs10980926	ZNF483	intronic	9	113333455	0.36	A	G	G	2.49	0.38	4.2E-11	A	2.4E-01	n
rs7821178	PXMP3	~181kb	8	78256392	0.34	A	C	A	2.36	0.40	3.0E-09	C	2.8E-01	n
rs1361108	C6orf173, TRMT11	~98kb, ~407kb	6	126809293	0.46	T	C	T	2.13	0.38	1.7E-08	C	3.0E-01	n
rs2243803	SLC14A2	~238kb	18	41210670	0.40	A	T	T	1.96	0.38	3.4E-07	T	3.3E-01	y
rs900145	ARNTL	~5 kb	11	13250481	0.30	C	T	T	2.34	0.41	1.6E-08	T	3.5E-01	y
rs1659127	MKL2	~28kb	16	14295806	0.34	A	G	G	2.43	0.41	4.0E-09	A	3.5E-01	n
rs12472911	LRP1B	intronic	2	141944979	0.20	C	T	T	2.54	0.48	1.5E-07	T	3.6E-01	y
rs1079866	INHBA	~250kb	7	41436618	0.15	G	C	C	3.95	0.52	5.5E-14	G	4.4E-01	n
rs7759938	LIN28B	~26kb	6	105485647	0.32	C	T	T	6.45	0.39	5.4E-60	C	4.4E-01	n
rs2002675	TRA2B, ETV5	~4kb, ~135kb	3	187112262	0.42	G	A	A	2.23	0.37	1.2E-09	G	4.6E-01	n
rs10423674	CRTC1	intronic	19	18678903	0.35	A	C	C	2.28	0.39	5.9E-09	C	5.0E-01	y
rs6589964	BSX	~18kb	11	122375893	0.48	A	C	A	2.68	0.38	1.9E-12	A	5.3E-01	y
rs2687729	EEFSEC	intronic	3	129377916	0.27	G	A	A	2.29	0.43	1.3E-07	A	5.3E-01	y
rs1364063	NFAT5	~10kb	16	68146073	0.43	C	T	T	2.13	0.38	1.8E-08	T	5.6E-01	y
rs17188434	NR4A2	~84kb	2	156805022	0.07	C	T	C	4.52	0.74	1.1E-09	C	5.9E-01	y
rs7642134	VGLL3	~70kb	3	86999572	0.38	A	G	A	2.41	0.38	3.5E-10	G	7.2E-01	n
rs6438424	3q13.32	intergenic	3	119057512	0.50	A	C	A	2.73	0.37	1.4E-13	A	7.3E-01	y
rs4840086	PRDM13, MCHR2	~145kb, ~160kb	6	100315159	0.42	G	A	G	2.11	0.38	2.4E-08	G	7.6E-01	y
rs7617480	KLHDC8B	intronic	3	49185736	0.22	A	C	C	2.42	0.44	2.8E-08	A	8.4E-01	n
rs6575793	BEGAIN	intronic	14	100101970	0.42	C	T	T	2.27	0.40	1.2E-08	T	8.6E-01	y
rs852069	PCSK2	~84kb	20	17070593	0.37	A	G	A	2.08	0.38	3.3E-08	G	8.8E-01	n
rs3743266	RORA	3'UTR	15	58568805	0.32	C	T	C	2.01	0.41	8.0E-07	T	8.9E-01	n
rs16938437	PHF21A	intronic	11	46009151	0.09	T	C	T	3.67	0.68	5.9E-08	C	9.7E-01	n
rs6762477	RBM6	intronic	3	50068213	0.44	G	A	A	2.54	0.45	1.6E-08	*data for rs6762477 unavailable in GIANT*		

[a] Indicates whether menarche decreasing and BMI increasing alleles are consistent (y=yes, n=no)

Supplementary Table 16: Association of menarche loci with height in ~130,000 adults in the GIANT consortium.

								Association with menarche				Association with adult height				
SNP	Nearest gene(s)	Distance from gene (kb)	Chr	Position (B36)	MAF	Minor allele	Major allele	Menarche decreasing allele	Beta (weeks/allele)	se	P-value	Height decreasing allele	Zscore per allele	se	P-value	Direction consistent[a]
rs7759938	LIN28B	~26kb	6	105485647	0.32	C	T	T	6.45	0.39	5.4E-60	T	0.042	0.005	8.7E-18	y
rs1361108	C6orf173, TRMT11	~98kb, ~407kb	6	126809293	0.46	T	C	T	2.13	0.38	1.7E-08	C	0.035	0.005	1.9E-14	n
rs7821178	PXMP3	~181kb	8	78256392	0.34	A	C	A	2.36	0.40	3.0E-09	C	0.023	0.005	1.6E-06	n
rs1659127	MKL2	~28kb	16	14295806	0.34	A	G	G	2.43	0.41	4.0E-09	G	0.024	0.005	2.9E-06	y
rs2090409	TMEM38B	~400kb	9	108006909	0.31	A	C	A	4.73	0.39	2.2E-33	A	0.020	0.005	2.8E-05	y
rs1364063	NFAT5	~10kb	16	68146073	0.43	C	T	T	2.13	0.38	1.8E-08	T	0.018	0.005	5.9E-05	y
rs2002675	TRA2B, ETV5	~4kb, ~135kb	3	187112262	0.42	G	A	A	2.23	0.37	1.2E-09	A	0.017	0.005	2.2E-04	y
rs16938437	PHF21A	intronic	11	46009151	0.09	T	C	T	3.67	0.68	5.9E-08	T	0.027	0.008	9.5E-04	y
rs10980926	ZNF483	intronic	9	113333455	0.36	A	G	G	2.49	0.38	4.2E-11	G	0.015	0.005	1.7E-03	y
rs6589964	BSX	~18kb	11	122375893	0.48	A	C	A	2.68	0.38	1.9E-12	A	0.014	0.005	2.5E-03	y
rs6438424	3q13.32	intergenic	3	119057512	0.50	A	C	A	2.73	0.37	1.4E-13	A	0.013	0.004	4.0E-03	y
rs900145	ARNTL	~5 kb	11	13250481	0.30	C	T	T	2.34	0.41	1.6E-08	T	0.013	0.005	9.4E-03	y
rs1079866	INHBA	~250kb	7	41436618	0.15	G	C	C	3.95	0.52	5.5E-14	C	0.016	0.006	1.5E-02	y
rs17188434	NR4A2	~84kb	2	156805022	0.07	C	T	C	4.52	0.74	1.1E-09	C	0.021	0.009	1.7E-02	y
rs3914188	ECE2	3'UTR	3	185492742	0.27	G	C	G	2.21	0.43	2.6E-07	C	0.012	0.005	2.8E-02	n
rs4840086	PRDM13, MCHR2	~145kb, ~160kb	6	100315159	0.42	G	A	G	2.11	0.38	2.4E-08	G	0.010	0.005	3.2E-02	y
rs3743266	RORA	3'UTR	15	58568805	0.32	C	T	C	2.01	0.41	8.0E-07	C	0.010	0.005	4.2E-02	y
rs13187289	PHF15	~12kb	5	133877076	0.20	G	C	C	3.02	0.48	1.9E-10	C	0.012	0.006	4.3E-02	y
rs1398217	FUSSEL18	intronic	18	43006236	0.43	G	C	G	2.69	0.37	2.3E-13	G	0.009	0.005	6.1E-02	y
rs9939609	FTO	intronic	16	52378028	0.40	A	T	A	2.12	0.39	3.1E-08	A	0.008	0.005	6.4E-02	y
rs12472911	LRP1B	intronic	2	141944979	0.20	C	T	T	2.54	0.48	1.5E-07	C	0.010	0.006	6.6E-02	n
rs12617311	PLCL1	~195kb	2	199340810	0.32	A	G	A	3.03	0.42	6.0E-13	A	0.007	0.005	2.0E-01	y
rs633715	SEC16B	~44kb	1	176119203	0.20	C	T	C	2.63	0.47	2.1E-08	T	0.007	0.006	2.2E-01	n
rs2243803	SLC14A2	~238kb	18	41210670	0.40	A	T	T	1.96	0.38	3.4E-07	T	0.005	0.005	2.7E-01	y
rs2947411	TMEM18	~53kb	2	604168	0.17	A	G	G	2.84	0.51	1.7E-08	A	0.006	0.006	3.0E-01	n
rs17268785	CCDC85A	intronic	2	56445587	0.17	G	A	A	3.22	0.50	9.7E-11	A	0.006	0.006	3.1E-01	y
rs4929923	TRIM66	3'UTR	11	8595776	0.36	T	C	C	2.27	0.40	1.2E-08	C	0.004	0.005	3.6E-01	y
rs9635759	CA10	~94kb	17	46968784	0.32	A	G	G	2.97	0.41	7.3E-13	G	0.005	0.006	4.1E-01	y
rs466639	RXRG	intronic	1	163661506	0.13	T	C	T	4.20	0.57	1.3E-13	T	0.005	0.007	4.8E-01	y
rs10423674	CRTC1	intronic	19	18678903	0.35	A	C	C	2.28	0.39	5.9E-09	C	0.003	0.005	4.9E-01	y
rs6439371	TMEM108, NPHP3	~146kb, ~170kb	3	134093442	0.34	G	A	A	2.32	0.41	1.3E-08	G	0.003	0.005	5.4E-01	n
rs1862471	OLFM2	intronic	19	9861322	0.47	G	C	C	2.03	0.39	1.5E-07	C	0.003	0.005	5.7E-01	y
rs852069	PCSK2	~84kb	20	17070593	0.37	A	G	A	2.08	0.38	3.3E-08	G	0.002	0.005	6.2E-01	n
rs7359257	IQCH	intronic	15	65489961	0.45	A	C	C	1.73	0.36	1.9E-06	A	0.002	0.005	6.3E-01	n
rs757647	KDM3B	intronic	5	137735214	0.22	A	G	A	2.40	0.44	5.4E-08	G	0.003	0.005	6.3E-01	n
rs10899489	GAB2	intronic	11	77773021	0.15	A	C	C	3.09	0.54	8.1E-09	C	0.003	0.006	6.5E-01	y
rs7642134	VGLL3	~70kb	3	86999572	0.38	A	G	A	2.41	0.38	3.5E-10	A	0.002	0.005	6.8E-01	y
rs7617480	KLHDC8B	intronic	3	49185736	0.22	A	C	C	2.42	0.44	2.8E-08	A	0.002	0.005	7.4E-01	n
rs6575793	BEGAIN	intronic	14	100101970	0.42	C	T	T	2.27	0.40	1.2E-08	T	0.001	0.005	8.2E-01	y
rs9555810	C13orf16, ARHGEF7	~185kb, ~223kb	13	110979438	0.28	G	C	C	2.31	0.43	5.6E-08	G	0.001	0.005	8.5E-01	n
rs6762477	RBM6	intronic	3	50068213	0.44	G	A	A	2.54	0.45	1.6E-08	G	0.001	0.006	8.6E-01	n
rs2687729	EEFSEC	intronic	3	129377916	0.27	G	A	A	2.29	0.43	1.3E-07	G	0.001	0.005	9.0E-01	n

[a] Indicates whether menarche decreasing and height decreasing alleles are consistent (y=yes, n=no)

Supplementary Table 17: Association of menarche loci with height in ~130,000 adults in the GIANT consortium.

	n	beta (weeks/allele)	SE	p
Menarche risk allele score	5721	-1.76	0.30	4.6E-09
adjusted for mother's age	5721	-1.76	0.30	4.1E-09
adjusted for mother's age and BMI	5381	-1.74	0.30	9.4E-09
adjusted for mother's age and height	5641	-1.69	0.30	1.7E-08
adjusted for mother's age, BMI and height	5381	-1.73	0.30	9.0E-09

*Calculated as the sum of menarche-lowering alleles in each individual across 30 SNPs
Missing genotypes were imputed with the mean value in individuals with at least 18 succesfully genotyped SNPs

SUPPLEMENTARY NOTE

CONTENTS

STUDY INFORMATION

a) Stage 1 GWAS studies

AGES-Reykjavik Study: The Reykjavik Study cohort originally comprised a random sample of 30,795 men and women born in 1907-1935 and living in Reykjavik in 1967. A total of 19,381 people participated in the Reykjavik Study examination, a 71% recruitment rate. The study sample was divided into six groups by birth year and birth date within month. One group was invited to participate in all subsequent examinations, while one group was designated as a control group and was not included in examinations until 1991. Other groups were invited to participate in specific examinations of the study. Between 2002 and 2006, the AGES-Reykjavik Study re-examined 5764 survivors of the original Reykjavik Study. Successful genotyping was available for 1849 AGES women participants who were eligible for this study. The AGES-Reykjavik Study GWAS was approved by the National Bioethics Committee and the Data Protection Authority and also was covered under the MedStar Institutional Review Board. All subjects provided written informed consent.

Amish: The Old Order Amish are a closed founder population in Lancaster County, PA. Due to their unique immigration and ancestral history, all current living Old Order Amish can be connect via one single 13 generation pedigree[1,2]. Women included in this study were recruited as part of at least one of multiple studies performed in this population and are described elsewhere[3-7]. All study protocols were approved by the Institutional Review Board at the University of Maryland, Baltimore and informed consent was obtained from each participant. Physical examinations were performed at the Amish Research Clinic in Strasburg, PA and a reproductive health questionnaire was completed by self report. Presenting pregnant or within 6 months postpartum were common exclusion criteria among all study designs.

ARIC: The ARIC study is a multi-center prospective investigation of atherosclerotic disease in a bi-racial population[8]. Men and women aged 45-64 years at baseline were recruited from 4 communities: Forsyth County, North Carolina; Jackson, Mississippi; suburban areas of Minneapolis, Minnesota; and Washington County, Maryland. A total of 15,792 individuals participated in the baseline examination in 1987-1989, with four follow-up examinations in approximate 3-year intervals, during 1990-1992, 1993-1995, and 1996-1998. Only White women with genotype data and age at menarche between 9 and 17 years of age were included in this analysis (N=4247). This study was approved by the institutional review board at each field center, and this analysis was approved by the University of North Carolina at Chapel Hill School of Public Health Institutional Review Board on research involving human subjects. All subjects provided written informed consent.

The 1958 British Birth Cohort (B58C): The 1958 Birth Cohort (also known as the National Child Development Study) is a national population sample followed periodically from birth to age 44-45 years. It includes all births in England, Wales and Scotland, during one week in 1958. Age at menarche was derived from reports at examination at the age of 16[9]. Genotyping of this study was previously performed as a part of the Wellcome Trust Case Control Consortium (WTCCC) and the Type 1 Diabetes Genetics Consortium (T1DGC) and has been described previously[10-12]. The current analysis included 1584 individuals that passed the quality control criteria and that had data on age at menarche.

Cohorte LAUSannoise (CoLaus): CoLaus is a cross-sectional study of a random sample of 6188 European adults (including 2,976 women), aged 35–75 years, living in Lausanne, Switzerland[13]. Recruitment took place between April 2003 and March 2006. Only individuals with four grandparents of European origin were included in the study. Participants provided a detailed health questionnaire, underwent a physical exam and donated blood after a 12-hr fasting period for clinical chemistry and genetic analyses. Following exclusions due to quality control criteria and missing data, 2,874 women were included in the genome-wide analyses. In all studies, age at menarche to the nearest completed whole year was ascertained at baseline by questionnaire. The CoLaus study was sponsored in part by GlaxoSmithKline, and all participants were duly informed about this sponsorship, and consented for the use of biological samples and data by GlaxoSmithKline and its subsidiaries; the study was approved by the Local Ethics committee.

deCODE Genetics (Iceland): Self-reported age at menarche was available from 39,728 Icelanders. The information had been collected in a nationwide cancer screening program through the Cancer Detection Clinic at the Icelandic Cancer society since 1964. The question referred to age at previous birthday before onset of the first menstruations and the individuals had a reported age at first menstruation between 8 and 20 years. Of these individuals, 15,864 were genotyped on an Illumina 317K/ 370 K SNP chip in one of several genome-wide association studies recently conducted by deCODE Genetics. All of these studies were approved by the Data Protection Commission of Iceland and the National Bioethics Committee of Iceland. Written informed consent was obtained from all participants. Personal identifiers associated with phenotypic information and blood samples were encrypted using a third-party encryption system as previously described. Only individuals with a genotype yield over 98% were included in the study.

Danish National Birth Cohort: DNBC is a population-based cohort of 101,042 pregnancies, recruited in the years 1996-2002[14]. All participating women underwent thorough phenotype characterization based on information from four computer-assisted telephone interviews conducted during pregnancy (two interviews) and after delivery (two interviews). During the first interview women were asked “How old were you when you had your first menstrual period?” GWAS data were generated for 3,840 individuals from the DNBC (mothers

and their children) in a study of prematurity and its complications (Principal investigator Jeff Murray) within the Gene Environment Association Studies (GENEVA) consortium. Age at menarche between 9 and 17 years and genome-wide genotype and imputed data were available for 1,748 women. The DNBC study protocol was approved by the Danish Scientific Ethical Committee and the Danish Data Protection Agency.

Estonian Genome Center, University of Tartu (EGCUT): The Estonian cohort is from the population-based biobank of the Estonian Genome Project of University of Tartu. The project was conducted according to the Estonian Gene Research Act and all participants signed the broad informed consent[15] (www.geenivaramu.ee). The current cohort size is over 43,000, from 18 years of age and up, which reflects closely the age distribution in the adult Estonian population. Participants were randomly selected from individuals visiting GP offices or hospitals and were recruited by general practitioners (GP) and physicians. Each participant filled out a Computer Assisted Personal interview, which included personal data (place of birth, place(s) of living, nationality etc.), genealogical data (family history, three generations), educational and occupational history and lifestyle data (physical activity, dietary habits, smoking, alcohol consumption, women´s health, quality of life). Anthropometric and physiological measurements were also taken. GWAS was performed on 2,700 randomly selected individuals[16] with the Illumina HumanHapCNV370 array, according to the Illumina protocol (www.illumina.com) in the Estonian Biocenter Genotyping Core Facility. Age at menarche between 9 and 17 years were available for 987 females for the genome wide meta-analyis stage of this project. Data on a further 196 women was available for in silico replication.

EPIC-Norfolk Obesity Case-Cohort: The European Prospective Investigation into Cancer and Nutrition (EPIC-Norfolk) cohort was initially designed to investigate the relationship between diet, cancer and chronic disease. The total study size was 25,639 men and women of European descent from Norfolk in the United Kingdom and aged between 39 and 79 years in 1993-1997[17]. The EPIC Obesity case-cohort study includes obesity cases and cohort controls. 1685 obese cases (718 women), defined as those with a body mass index >30 kg/m^2 , were randomly selected from the obese individuals within EPIC-Norfolk. The control-cohort consists of a further 2566 individuals (1364 women) randomly selected from the EPIC-Norfolk study. Age at menarche in completed whole years was ascertained at baseline in women by questionnaire. Following exclusions due to quality control criteria and missing data, data on 625 obese and 1,215 control women were available for genome-wide analysis. Ethical approval for the study was granted by the Norwich Local Research Ethics Committee. All subjects gave written informed consent.

ERF: The Erasmus Rucphen Family study is part of the Genetic Research in Isolated Population program. The study population essentially consists of one extended family of descendents from 20 related couples who lived in the isolate between 1850 and 1900 and had at least 6 children baptized in the community church. The

detailed information about ERF isolate can be found elsewhere[18]. The Medical Ethical Committee of the Erasmus Medical Center, Rotterdam approved the study and informed consent was obtained from all participants. Self-reported age at start of menarche was assessed by a questionnaire and genome-wide and imputed data were available for 1103 women.

The Framingham Heart Study began in 1948 to study determinants of cardiovascular disease and other major medical conditions[19,20]. In 1971, Offspring of the Original Cohort participants and Offspring spouses were enrolled into the Framingham Offspring Study. Offspring participants, including 2641 women (mean age 36 years), have been examined approximately every 4 to 8 years[21,22]. From 2002 to 2005, 4095 adults including 2182 women (mean age 40 years) with at least one parent in the Offspring Study were enrolled in the Framingham Third Generation cohort[23]. Women were queried about menarche at the second Offspring examination (1979 to 1982) and at the first Third Generation examination with the following questions: "*Age at start of menses*" and "*How old were you when you had your first menstrual period (menses)?"*, respectively. The self-reported age at first period was recorded. Offspring women participating in the Framingham Osteoporosis Study (1996 – 2001) were asked about menarche with the following query: *"About how old were you when you had your first menstrual period?"*. The self-reported data from the Osteoporosis examination was used (n=214) if menarche data was not available from Offspring examination two. There were 1777 Offspring Cohort and 2024 Third Generation women who reported an age at menarche between 9 and 17 years with genotyping available.

SNP weights for 10 principal components (PCs) were inferred using a maximal set of independent individuals; the PCs for the remaining individuals were computed using the SNP weights obtained from the unrelated set of individuals. The first PC (PC1) was significantly associated with age at menarche ($P<0.01$), and therefore was included as a covariate in all SNP association analyses. In addition, we adjusted for birth cohort by decade. Linear mixed effects models were used to account for familial correlations. Each SNP was tested for association with age at menarche using an additive genetic model.

HBCS: Helsinki Birth Cohort Study (HBCS) includes 8760 subjects born in Helsinki between 1934 and 1944. A representative subset of 928 males and 1075 females participated in a clinical study between 2000 and 2002 focusing on cardiovascular and metabolic outcomes. During the clinical visit information on age at menarche was collected with a questionnaire[24]. The current study is restricted to 976 females for which successful genotyping on Illumina 670 Quad arrays (modified from Illumina Infinium 610K arrays) and data on age of menarche were available.

Health 2000 cases and controls: The Health 2000 (H2000), is a health interview/examination survey carried out by the National Institute for Health and Welfare in Finland from fall 2000 to spring 2001, with a nationally representative sample of 10,000 individuals drawn from the Finnish population aged 18 and older. The main topics of the study were health status, major chronic conditions, functional ability and limitations, determinants of health, and use of health care[25]. Data on female reproductive health, including age at menarche, was collected with a separate questionnaire. From a sub-cohort of 6,000 individuals representative of the Finnish population over age 30, roughly 1000 non-diabetic subjects meeting the IDF criteria for metabolic syndrome and control cohort of 1000 subjects matched for sex, age and residence, were selected for GWAS analyses. The current study is restricted to 457 females from the control group and 465 females from the metabolic syndrome case group for which successful genotyping on Illumina 670 Quad arrays (modified from Illumina Infinium 610K arrays) and data on age of menarche were available.

For all study subjects participating in the different Finnish cohort studies (HBCS, NFBC and Health 2000), informed consent was obtained using protocols approved by the corresponding local Ethical Committees. Furthermore, the studies were approved by the national Data Protection Boards where relevant.

InCHIANTI: The InCHIANTI study is a population-based epidemiological study aimed at evaluating factors that influence mobility in the older population living in the Chianti region of Tuscany, Italy. Details of the study have been previously reported[26]. Briefly, 1616 residents were selected from the population registry of Greve in Chianti (a rural area; 11,709 residents with 19.3% of the population greater than 65 years of age) and Bagno a Ripoli (Antella village near Florence; 4704 inhabitants, with 20.3% greater than 65 years of age). The participation rate was 90% (n= 1453) and participants ranged between 21–102 years of age. The study protocol was approved by the Italian National Institute of Research and Care of Aging Institutional Review. There were 85 parent-offspring pairs, 6 sib-pairs and 2 half-sibling pairs documented. We investigated any further familial relationships using IBD of 10,000 random SNPs using RELPAIR and uncovered 1 parent-offspring, 79 siblings and 13 half-sibling[27]. We utilized the correct family structure inferred from genetic data for all analyses.

Indiana: Genetic studies of bone density and related phenotypes in premenopausal women at Indiana have been ongoing since 1988, beginning with studies in twin pairs. This has expanded over time to include sibling pair linkage and association studies[28]. Peak bone mineral density as measured premenopausally in women and before age 60 in men is the primary quantitative phenotype of interest, specifically at the femoral neck and lumbar spine. The sample consists of European-American premenopausal sister pairs from Indiana, at least 20 years of age. The subjects were recruited without regard to bone density or other clinical phenotype. The exclusion criteria were limited to irregular menses or a history of pregnancy or lactation within three months

prior to enrollment, a history of chronic disease, current medications known to affect bone mass or metabolism, or inability to have BMD measured due to obesity. GWAS genotyping was performed by CIDR using the Illumina HumanHap 610 Quad version 1B platform, and the current analysis included all individuals with GWAS genotypes and age of menarche as measured by recall at their study visit.

Details of the **Nurses' Health Study (NHS)** cohorts have been described previously[29]. Briefly, the NHS was initiated in 1976, when 121,700 United States registered nurses between the ages of 30 and 55, residing in 11 larger U.S. states, returned an initial questionnaire reporting medical histories and baseline health-related exposures, including information related to reproductive history (age at menarche, age at first birth, parity, age at menopause etc.), and exposure to exogenous hormones (oral contraception or post-menopausal hormone replacement therapy). Biennial questionnaires with collection of exposure information on risk factors have been collected prospectively, and outcome data with follow-up of reported disease events are collected. From May 1989 through September 1990, we collected blood samples from 32,826 participants in the NHS cohort. Subsequent follow-up has been greater than 99% for this subcohort. Informed consent was obtained from all participants. The study was approved by the Institutional Review Board of the Brigham and Women's Hospital, Boston, MA, USA.

NHS breast cancer GWAS (CGEMS): The NHS nested breast cancer case-control study was derived from the 32,826 women in the blood subcohort who were free of diagnosed breast cancer at blood collection and followed for incidence disease until June 1, 2004. Breast cancer follow-up in the NHS was conducted by personal mailings and searches of the National Death Index. Controls were women not diagnosed with breast cancer during follow-up, and were one-to-one matched to cases based on age at diagnosis, blood collection variables (time of day, season, and year of blood collection, as well as recent (<3 months) use of postmenopausal hormones), ethnicity (all cases and controls are self-reported Caucasians), and menopausal status (all cases were postmenopausal at diagnosis). The 2,287 NHS participants included in the present analysis were from this nested breast cancer case-control study and were self-described Caucasians with genotype data available from the National Cancer Institute's Cancer Genetic Marker of Susceptibility (CGEMS) project[30]. There were 2270 women reporting age at menarche between ages 9-17 years with genotyping data available.

NHS type 2 diabetes (T2D) GWAS: NHS participants for the current T2D GWAS were also selected among those with a blood sample using a nested case-control design[31]. Diabetes cases were defined as self-reported diabetes confirmed by a validated supplementary questionnaire. For cases before 1998, diagnosis was made using criteria consistent with those proposed by the National Diabetes Data Group (NDDG)[32]. We used the American Diabetes Association diagnostic criteria for diagnosis of diabetes cases during the 1998 and 2000

cycles[33]. 98% of self-reported cases were confirmed by medical records review in this cohort[34]. Controls were defined as those free of diabetes at the time of diagnosis of the case and remained unaffected through follow-up (2006). Although controls were originally matched per case (by gender, year of birth, month of blood collection, and fasting status), matched pairs were broken because not all subjects gave informed consent for submission of their GWAS data to dbGaP. The current analysis included 3090 Caucasian women who had genotyping data and reported age at menarche between ages 9-17 years.

The NHS breast cancer GWA scan used the Illumina Infinium Sentrix HumanHap550 chip. Detailed methods related to the genotyping have been published previously[30]. Imputation of untyped genotypes was based on HapMap haplotype reference (release 21) using MACH software.

The NHS T2D GWA scan is a component of the Gene Environment-Association Studies (GENEVA) under the NIH Genes, Environment and Health Initiative (GEI). Genotyping was done at the Broad Center for Genotyping and Analysis using the Affymetrix Human 6.0 array (Santa Clara, CA) and the Birdseed calling algorithm[35]. Imputation of untyped genotypes was based on HapMap haplotype reference (release 22) using MACH software.

NFBC: The Northern Finland Birth Cohort 1966 (NFBC1966; http://kelo.oulu.fi/NFBC/pub/) is a prospective cohort study conducted in the two northernmost provinces in Finland, Oulu and Lapland. The study enrolled mothers living in the district who had estimated dates of delivery in year 1966. Altogether 12,231 births were included in the study, representing 96% of all births in these provinces. Data on the mothers' height and pre-pregnancy weight were collected from standard forms for the pregnancy follow-up and the maternity cards carried by all mothers. The offspring were followed up at 6 months, 1, 14 and 31 years of age. Data on age at menarche was obtained retrospectively by a postal questionnaire at age 31. Also at age 31, a representative sub-sample of the study subjects (cohort members still living in Northern Finland or in the capital area) were invited for clinical examination. At the clinical visit, height and weight were assessed. The participants (n=5654), also provided a fasting blood sample, from which DNA was extracted. The study protocol, the data collection protocol and the clinical measurement procedures of the complete cohort study have earlier been described in detail[36,37]. The current study is restricted to females for which successful genotyping was completed on Illumina Infinium 370cnvDuo arrays, as described by Sabatti et al (2009)[38], and for which age at menarche data were available.

NTR: As part of a longitudinal survey study of health, lifestyle and personality, twins and their family members registered with the Netherlands Twin Register (NTR) are approached every 2 to 3 years[39]. As part of a case-control study for major depression disorder, genotype information was obtained in 1940 NTR participants[40]. In

the surveys female participants were asked at what age they had their first menstrual period. Inconsistencies over time were checked. Age of menarche was available for 1051 participants.

QIMR: Data for age at menarche were available from two separate cohorts referred to as the Adult and Adolescent cohorts. The adult data were gathered from a number of studies carried out between 1980 and 1995. Many of these studies were follow-up studies and so there is a large overlap in participants. There are two main Adult cohorts. The first study, known as The Canberra Study, involved twins from the Australian Twin Registry who were aged between 17 and 88 when they were surveyed between 1980 and 1982. The twins were mailed a health questionnaire which included a number of questions about their reproductive history including a question about their age at menarche -"How old were you (in years and months) when you had your first menstrual period? A second cohort was recruited in 1989 involving twins born between 1964 and 1971 and their first degree relatives. They answered a similar questionnaire to the one answered by the Canberra cohort. The adult cohorts provided a total of 2,256 individuals with age at menarche to the analysis

Adolescent twins and their siblings were drawn from the adolescent cohorts that had been recruited as part of ongoing studies of melanoma risk factors[41] and cognition[42]. The protocol for obtaining information on age at menarche has been described in a previous paper[43]. Due to additional data collection, this study includes more individuals than the previous linkage analysis. The young age of the cohort meant that there was a significant amount of censoring in the data. All censored individuals who were younger than the mean age at menarche in the sample at the age of their last interview, were removed from the analysis. After removal of non-genotyped individuals, individuals who were removed in the genotypic QC process, and those who were phenotypic outliers there were 1,274 individuals with phenotype and genotype information remaining. Of these, 2 individuals had a censored age at menarche and these were excluded from the analysis. In cases where there was more than one measure of age at menarche, the earliest measure was used as this was assumed to be closest to the true age, and hence the most accurate. Details of the genotyping and imputation are given elsewhere[44].

Rotterdam Study I, II, and III are ongoing prospective population-based cohort studies, focus on chronic disabling conditions of the elderly in the Netherlands. In summary, men and women aged 55 years or older, living in Ommoord, a suburb of Rotterdam, the Netherlands, were invited to participate[45]. Self-reported age at menarche was assessed by questionnaire. Age at menarche between 9 and 17 years (collected retrospectively) and genome-wide genotype and imputed data were available for 3175 (RSI), 1119 (RSII) and 1112 (RS3) women. GWA analysis was performed using GRIMP[46].

SAGE: The Study of Addiction: Genetics and Environment is funded as part of the Gene Environment Association Studies initiative (GENEVA) supported by the National Human Genome Research Institute (dbGaP

study accession phs000092.v1.p1). Subjects were selected from three large, complementary datasets: the Collaborative Study on the Genetics of Alcoholism (COGA), the Family Study of Cocaine Dependence (FSCD), and the Collaborative Genetic Study of Nicotine Dependence (COGEND). The Institutional Review Board at each contributing institution reviewed and approved the protocols for genetic studies under which all subjects were recruited. All subjects completed a comprehensive psychiatric interview that was based on the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA)[47]. As part of this assessment, female subjects were asked "At what age did you have your first menstrual period?" Data are available for 1376 subjects; mean age at menarche was 12.8. For additional description of the studies, see http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000092.v1.p1.

Samples were genotyped at the Johns Hopkins Center for Inherited Disease Research (CIDR). Data were released for 4,189 study samples. Study samples, including 49 study duplicates, were plated and genotyped together with 135 HapMap controls (86 CEU; 49 YRI). Genotyping was performed using Illumina Human1Mv1_C BeadChips (Illumina, San Diego, CA, USA) and the Illumina Infinium II assay protocol[48]. Allele cluster definitions for each SNP were determined using Illumina BeadStudio Genotyping Module version 3.1.14 and the combined intensity data from the samples. Strict quality control standards were implemented and genotypes were released by CIDR for 1,040,106 SNPs (99.15% of attempted). The mean non-Y SNP call rate and mean sample call rate was 99.7% for the released CIDR dataset. Study duplicate reproducibility was 99.98%. Further extensive cleaning was undertaken to insure high quality genotyping by examining batch effects, potential chromosomal anomalies, and Mendelian errors (Laurie et al., under review).

SNPs with an allele frequency > 1% in either the European or African descent populations were analyzed (948,658 SNPs). A SNP call rate of 98% was required. Hardy Weinberg equilibrium (HWE) was tested and SNPs that deviated from HWE ($p < 10–4$) were excluded. The final number of subjects included in analyses was 3,834. Individuals were dropped if there was potential sample misidentification, sample relatedness, or other misspecification (N=171).

SardiNIA: The SardiNIA genome wide association study has been described in detail previously[49,50]. Briefly, the GWA study examined a total of 4,305 related individuals participating in a longitudinal study of aging-related quantitative traits in the Ogliastra region of Sardinia, Italy. Genotyped individuals had four Sardinian grandparents and were selected for genotyping without regard to their phenotypes. Among the individuals examined, 1,412 were genotyped with the Affymetrix Mapping 500K Array Set. A total of 356,359 autosomal SNPs met the quality control criteria and were used as input for the imputation procedure using the software MACH[51,52]. The remaining 2,893 individuals were genotyped with the Affymetrix Mapping 10K Array. These individuals were mostly offspring and siblings of the 1,412 individuals that were genotyped with the Affymetrix

Mapping 500K Array Set. We took advantage of the relatedness among individuals to impute missing genotypes in these additional individuals; we identified large stretches of chromosome shared within each family and probabilistically "filled-in" genotypes within each stretch whenever one or more of its carriers was genotyped with the 500K Array Set[51,53]. In order to more efficiently evaluate identity-by-descendent states at non-overlapping markers, 436 individuals out of the 1,412 were also genotyped with the 10K Array. Among the 4,305 genotyped individuals, 2158 women were analysed for age at menarche.

TwinsUK: The TwinsUK cohort consisted of a group of twins ascertained to study the heritability and genetics of age-related diseases (www.twinsUK.ac.uk). These unselected twins were recruited from the general population through national media campaigns in the UK and shown to be comparable to age-matched population singletons in terms of disease-related and lifestyle characteristics[54,55].
The TwinsUK II and III cohorts consist of twins from the adult twin British registry, also shown to be representative of singleton populations and the United Kingdom population[56]. Age at menarche was assessed by questionnaire and genome-wide genotype and imputed data were available for 2276 (TwinsUK), 671 (TwinsUKII) and 1016 (TwinsUKIII) women. Ethics approval was obtained from the Guy's and St. Thomas' Hospital Ethics Committee. Written informed consent was obtained from every participant to the study.

TwinsUK samples were typed with the Infinium 610k assay (Illumina, San Diego, USA) at two different centers, and namely the Center for Inherited Diseases Research (USA) and the Wellcome Trust Sanger Institute. We pooled the normalised intensity data and called genotypes on the basis of the Illluminus algorithm. No calls were assigned if the most likely call was less than a posterior probability of 0.95. Validation of pooling was done by visual inspection of 100 random, shared SNPs for overt batch effects; none were observed. We excluded SNPs that had a low call rate (≤ 90%), Hardy-Weinberg p values < 10−4 and minor allele frequencies < 1%. We, also removed subjects where genotyping failed for >2 % of SNPs. The overall genotyping efficiency of the GWA was 98.7 %. Imputation of genotypes was carried out using the software IMPUTE[57].

WGHS: The Women's Genome Health Study (WGHS) is a prospective cohort of female healthcare professionals, aged 45 or older at baseline, who provided baseline blood sample and consent for blood based analysis in the Women's Health Study (WHS), a randomized, placebo controlled trial of aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer. A complete description of the WGHS has been published previously[58].

All information about reproductive aging was determined by self-report questionnaire at baseline and subsequent follow-up . For age of menarche, participants were asked "''At what age did your menstrual periods begin?'' with response categories ''9 or younger; 10; 11; 12; 13; 14; 15; 16; 17 or older.'' For age of

natural menopause, participants were asked ''Have your menstrual periods ceased permanently?'' If yes, ''At what age did your natural periods cease?'' and ''For what reason did your periods cease?'' with response categories ''Surgical; Radiation or Chemotherapy; Natural.'' Age at natural menopause was assessed in the baseline questionnaire for postmenopausal women at baseline, and updated in subsequent questionnaires for premenopausal women at baseline. In the current analysis all WGHS participants had passed through menopause. Women who reported menopause before 40 or after 60 were excluded.
Association testing for reproductive aging phenotypes was performed with Mach2Qtl v. 1.0.4.

Among WGHS participants, genotyped data was collected using the Illumina HumanHap300 Duo "+" platform, for which the "+" or custom content included SNPs chosen for suspected biological consequences as well as for increased coverage of genes related to cardiovascular disease. In final genotype data included 22,054 participants whose self-reported European ancestry was confirmed by principal component analysis in PLINK[59]. All of these samples had genotype information for >98% of the SNPs; all SNPs had complete information for >90% of the samples and deviations from Hardy-Weinberg equilibrium not exceeding $p < 10^{-6}$ in significance. Imputation of genotypes for a total of > 2.5 million SNPs was performed with MACH v. 1.0.16 (http://www.sph.umich.edu/csg/abecasis/MaCH/index.html) using linkage disequilibrium relationships from the HapMap CEU population release 22. Individuals for association testing in the current analysis were selected from this subset of WGHS participants on the basis of phenotype availability. Association testing for reproductive aging phenotypes was performed with Mach2Qtl v. 1.0.4

b) Replication Studies

The Avon Longitudinal Study of Parents and Children (ALSPAC) mothers
The Avon Longitudinal Study of Parents and Children (ALSPAC) is a prospective study that has been described in detail elsewhere[60] (http://www.alspac.bris.ac.uk). Briefly, 14,541 pregnant women living in one of three Bristol-based health districts in the former County of Avon with an expected delivery date between April 1991 and December 1992 were enrolled in the study. This represented 80–90% of the eligible population. Individuals of known non-white ethnic origin were excluded from all analyses. DNA was collected from mothers as described previously [61]. Genotypes for SNPs and age at menarche data were available in up to 6118 mothers. Mother's recalled age at menarche in completed whole years and adult height were obtained by questionnaires. Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee and Local Research Ethics Committees.

The Bogalusa Heart Study (BHS):
Between 1973 and 2008, 9 cross-sectional surveys of children aged 4-17 years and 10 cross-sectional surveys of adults aged 18-48 years, who had been previously examined as children, were conducted for CVD risk factor

examinations in Bogalusa, Louisiana. Collection of age at menarche information in the BHS has been previously described[62]. Briefly, girls in the 3rd grade and up were interviewed individually about menstrual history by a registered nurse during the collection of anthropometric measures, health habits, and cardiovascular risk factors. In the ongoing Longitudinal Aging Study funded by NIH and NIA since 2000, there are 1,202 subjects who have been examined 4-14 times from childhood to adulthood and have DNA available for GWA genotyping. Based on the analysis of identity-by-state (IBS) sharing from whole genome genotyping data, we focus on a subset of 343 genotyped women who are of European ancestry, unrelated, and have information about the onset of menarche.

We genotyped 1,202 BHS samples using the Illumina Human610 Genotyping BeadChip[63], and HumanCVD BeadChip[64]. Genotypes were called using a clustering algorithm in Illumina's BeadStudio software. Three samples on the 610 array gave poor results (call rates <99%) and were discarded from the study. In addition, 3 samples had a different estimated gender from genotype data versus gender provided with the phenotype data and were also discarded. SNPs with call rates <90% were discarded, and SNPs with call rates between 90-95% or cluster separation score < 0.3 were manually inspected and cluster positions were edited if needed. We removed approximately 30,000 SNP loci (4.9%) due to poor performance. The final average sample call rate was 99.95% for the 610 BeadChip, and 99.32% for the CVD BeadChip. We assessed reproducibility by genotyping 29 samples in duplicate (18 known replicates, 11 blind replicates), and observed >99.99% identical genotype calls on both BeadChips. Finally we observed 99.98% genotype concordance in 12,581 overlapping SNPs between the 610 and CVD BeadChips. Genotypes were imputed to HapMap release 22 CEU haplotypes using MACH v.1.0.16 (http://www.sph.umich.edu/csg/abecasis/MACH/index.html).

EGCUT (see Stage 1 GWAS study information)

INGI- Carlantino & Friuli Venezia Giulia: Carlantino is a small village in the Province of Foggia in southern Italy that was settled in by founders at the end of sixteenth century. The census in 1,595 counted 10 households in the village. Carlantino has a present-day population of 1,519 inhabitants, and three different surnames account for the majority of living individuals. The endogamy rate, calculated during past century, was 99.5%. Friuli Venezia Giulia: we analysed 4 isolated villages in Northern Italy in the region of Friuli Venezia Giulia. Genotyping was performed using the Illumina INFINIUM 370k CNV array, and imputation was performed using MACH. SNPs were analysed for association with age at menarche using ProbABEL on 322 (Carlantino) and 338 (FVG) women with data on age at menarche.

INGI – Val Borbera: The INGI-Val Borbera population is a collection of 1664 genotyped samples collected in the Val Borbera Valley, a geographically isolated valley located within the Appennine Mountains in NorthWest

Italy[65]. The valley is inhabited by about 3000 descendants from the original inhabitants, living in 7 villages along the valley and in the mountains. The valley was inhabited by about 10,000 people in the 19th century when endogamy was >80% . Around 1930, the population started to decrease due to emigration to South America. Participants were healthy people between 18 and 102 years of age that had at least one grandfather living in the valley. Information on participants was collected during an interview using a standardized medical questionnaire. A total of 910 women declared to have undergone menarche between the age of 9 and 17 (none declared an age at menarche outside this range). Genotyping was performed on an Illumina array 370k Quad v3 and missing data was imputed using MACH. Association testing was conducted using ProbABEL, whilst the variance explained by genetic variants was determined using the GenABEL package within R.

KORA F3 and S4: The KORA study is a series of independent population-based epidemiological surveys of participants living in the region of Augsburg, Southern Germany[66]. All survey participants are residents of German nationality identified through the registration office and were examined in 1994/95 (KORA S3) and 1999/2001 (KORA S4). In the KORA S3 study 4,856 subjects (response 75%), and in KORA S4 in total 4,261 subjects have been examined (response 67%). 3,006 subjects participated in a 10-year follow-up examination of S3 in 2004/05 (KORA F3). For KORA F3 we selected 1,644 subjects of these participants while for KORA S4 we randomly selected 1,814 subjects. Informed consent has been given by all participants. The study has been approved by the local ethics committee.

Genotyping for KORA F3 was performed using Affymetrix 500K Array Set consisting of two chips (Sty I and Nsp I). The KORA S4 samples were genotyped with the Affymetrix Human SNP Array 6.0. Hybridisation of genomic DNA was done in accordance with the manufacturer's standard recommendations. Genotypes were determined using BRLMM clustering algorithm (Affymetrix 500K Array Set) and Birdseed2 clustering algorithm (Affymetrix Array 6.0). For quality control purposes, we applied a positive control and a negative control DNA every 48 (KORA F3) samples or 96 samples (KORA S4). On chip level only subjects with overall genotyping efficiencies of at least 93% were included. In addition the called gender had to agree with the gender in the KORA study database. Imputation of genotypes was performed with the software MACH v1.0.9 (KORA F3) and MACH v1.0.15 (KORA S4) based on HapMap II and analyses were performed in R version 2.8.0.

Orcades: The Orkney Complex Disease Study (ORCADES) is an ongoing family-based, cross-sectional study in the isolated Scottish archipelago of Orkney. Genetic diversity in this population is decreased compared to Mainland Scotland, consistent with the high levels of endogamy historically.
Data for participants from a subgroup of ten islands were used for this analysis. Fasting blood samples were collected and over 200 health-related phenotypes and environmental exposures were measured in each

individual. All participants gave informed consent and the study was approved by Research Ethics Committees in Orkney and Aberdeen.

We genotyped 318,237 SNPs for each individual using the Illumina HumanHap300 beadchip. Alleles were called in BeadStudio using Illumina cluster files. Subjects were excluded if they fulfilled any of the following criteria: genotypic call rate <97%, mismatch between reported and genotypic sex, unexpectedly low genomic sharing with first degree relatives, excess autosomal heterozygosity, or outliers identified by IBS clustering analysis. We excluded SNPs on the basis of minor allele frequency (<0.01), HWE (P<10^-5), call rate (<97%). Pregnant women were excluded from the study. MACH v1.0.15 was used to impute over 2 million SNPs from HapMap build 36. Analyses were implemented using the GenABELand ProbABEL R libraries.

Raine: Recruitment of the Western Australian Pregnancy (Raine) cohort has previously been described in detail[67]. In brief, between 1989 and 1991 2,900 pregnant women were recruited prior to 18-weeks gestation into a randomised controlled trial to evaluate the effects of repeated ultrasound in pregnancy. Recruitment predominantly took place at King Edward Memorial Hospital (Perth, Western Australia). Ninety percent of eligible women agreed to participate in the study. Their 2,868 babies have been followed from recruitment at the average ages of one, two, three, five, eight, ten and 14. Most of the children are of Caucasian ethnicity (82% have two Caucasian parents). Month and year of first menstrual period for girls was recorded. Genotyping was performed using the Illumina 660w quad array and imputation was performed using MACH. Association testing was performed using R (version 2.6.2).

SASBAC: The Swedish and Singapore Breast Association Consortium is a case-control study of breast cancer that has been described previously[68,69]. After exclusions of related individuals and duplicates, ethnic outliers, women without age at menarche and age at menarche outside the range of 9-17 years, data on 723 cases and 685 controls with genome-wide data (call rate>96%) were available. Analyses were performed in SNPtest and STATA 11.0.

SEARCH: The SEARCH ovarian cancer study is an ongoing, population-based ovarian cancer case–control study covering the regions served by the East Anglia and West Midlands cancer registries in the UK and has been described previously[70]. 1126 cases were included in this analysis with genotype data available and age at menarche between 9 and 17 years. Analyses were performed in STATA 10.0.

STR_MZtwins (TWINGENE): Between the years 2004 and 2008 population wide collection of blood on 12,600 twins born 1958 or earlier has been undertaken in a project called TwinGene[71]. The aim of the TwinGene project has been to systematically transform the oldest cohorts of the Swedish Twin Registry (STR) into a

molecular-genetic resource. Beginning in 2004 about 200 twins were contacted each month until the data collection was completed in 2008. When the signed consent forms where returned, the subjects were sent blood sampling equipment and asked to contact a local health facility for blood sampling. Subjects living in vicinity to the cities of Stockholm, Gothenburg, Malmö or Västerås were given the option of visiting hospital blood sampling facilities, in which case the health checkup were omitted. The study population was recruited among twins participating in the Screening Across the Lifespan Twin Study (SALT) which was a telephone interview study conducted in 1998-2002. Other inclusion criteria were that both twins in the pair had to be alive and living in Sweden. Subjects were excluded from the study if they preciously declined participation in future studies or if they had been enrolled in other STR DNA sampling projects. Menopausal information was collected from the SALT interview. In 302 MZ pairs genome-wide array (Illumina 317K) genotyping has been performed. Among these, information on age at menarche was available for at least one of the twins in the pair for 302 pairs. For pairs in which information about menopause were available for both the average within-pair value was used.

VIS, KORCULA and SPLIT: The VIS study, Croatia, is a family-based, cross-sectional study in the isolated island of Vis that included 1,056 examinees aged 18-93. The KORCULA study, Croatia, is a family-based, cross-sectional study in the isolated island of Korcula that included about 965 examinees aged 18-95. The SPLIT study, Croatia, is an ongoing population-based, cross-sectional study in the Dalmatian City of Split that included about 535 examinees aged 18-95. Studies were genotyped using Illumina HAP300v1 (VIS) or Ilumina HAP370CNV (Korcula and SPLIT) and imputation for all studies was performed using MACHv1.16. Analyses were performed using R, GenABEL and ProbABEL.

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